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PANCREATIC ENZYMES IN THE DUODENAL JUICE IN THE CELIAC SYNDROME

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NEW YORK

The clinical diagnosis of cystic fibrosis of the pancreas, especially before the appearance of the associated pulmonary lesions, presents real difficulties. Experience has shown that the infection of the respiratory tract, once well established, does not often yield to treatment. A means of confirming the diagnosis in suspected cases would make it possible to attempt early dietary and vitamin therapy with some hope of success. Theoretically, the most direct method of diagnosis of pancreatic deficiency would be the assay of the pancreatic enzymes in the duodenal juice. On anatomic grounds one would expect the enzymes to be absent or of low concentration in all infants with pancreatic fibrosis and present in all other infants, with or without the celiac syndrome. However, the clinical similarity between cases of pancreatic fibrosis and cases of the celiac syndrome without anatomic change in the pancreas suggests the possibility of a functional change in the pancreas in the latter group. The present investigation was therefore undertaken for the purpose of determining the concentrations of pancreatic trypsin, lipase and amylase in the duodenal juice of infants and children with cystic fibrosis of the pancreas, with comparable observations on a series of infants with chronic diarrhea of unknown cause, a group with idiopathic steatorrhea and a series of controls without digestive or nutritional disorder. The serum amylase, too, was determined for many of the children, in the hope that this relatively simple procedure might be of diagnostic value.

Several previous studies on the pancreatic secretion in normal infants are recorded. The pioneer work was done in 1912 by Hess [1] who showed by qualitative tests that all three enzymes are present in early infancy.

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1. Hess, A. F.: The Pancreatic Ferments in Infants, Am. J. Dis. Child. 4:205 (Oct.) 1912.

Davison [2] in 1925 studied the trypsin and amylase in 6 normal infants and in 8 infants convalescing from diarrhea. The figures which he gives show a wide range of values, with a lower average value for amylase in the latter group. Stroe, Stroe and Théodorini [3] have also recorded a lower concentration of amylase in infants who had had diarrhea.

Klumpp and Neale [4] studied the lipase, trypsin and amylase in a series of 74 infants and children ranging in age from 1 month to 12 years. They concluded that the concentration of amylase was lower during the first year than in later childhood, that it reached a peak between the ages of 6 and 9 years and that it was somewhat lower in older children and adults. Venuti [4a] found no significant change in enzyme assays of the duodenal juice during the first year. The diagnosis of congenital pancreatic deficiency by means of enzyme studies on the duodenal juice has been recorded several times.[5]

METHODS

Means of Obtaining Duodenal Juice.—The commercial duodenal tubes were found to have tips which are too large, especially too long, for convenient use in small infants. A highly satisfactory tube was constructed in the laboratory from no. 12 French catheter tubing. A solid dumbbell-shaped metal tip, less than 1 cm. in length and 4 mm. in diameter, was tied with silk into the lower end, and perforations were made in the distal 5 cm. of the tube. The upper end of the tube was supplied with a small bakelite adapter attached to a short length of rubber tubing of a size which would fit a 20 cc. Luer syringe. No attempt was made to use an Abbott tube, because it was thought that its use would prolong the procedure, especially in the marasmic infants with low grade motility.

All patients were well hydrated but fasting at the time of the examination. For infants on a four hour feeding schedule, the 6 a. m. formula was given as usual and water was urged until one hour before the examination, after which time nothing was given by mouth. The tube was passed between 9:30 and 10:30 a. m., or at about the time when the next feeding was due. In the case of older infants and children, breakfast was omitted but water was urged until one hour before the examination, which took place between 8:30 and 10:30 a. m. The tube was

2. Davison, W. C.: Duodenal Contents of Infants in Health, and During and Following Diarrhoea, Am. J. Dis. Child. **29**:743 (June) 1925.

3. Stroe, S.; Stroe, M., and Théodorini, P.: Les ferments pancréatiques au cours des troubles digestifs de la première enfance, Nourrisson **17**:193, 1929.

4. Klumpp, T. G., and Neale, A. V.: The Gastric and Duodenal Contents of Normal Infants and Children, Am. J. Dis. Child. **40**:1215 (Dec.) 1930.

4a. Venuti, A.: Esame dell'attività dei fermenti pancreatici nel lattante per mezzo del sondaggio duodenale, Riv. di clin. pediat. **29**:17, 1931.

5. Benoit, W.: Hyperinsulinismus bei eingeborener Atresie des Pankreasganges, Endokrinologie **16**:313, 1935. Tiling, W.: Angeborene Pankreasgangsatresie und Inselhypertrophie: Ein Beitrag zur Diagnostik der Pankreaserkrankungen, Arch. f. Kinderh. **106**:9, 1935. Siwe, S. A.: Ueber die exokrine Funktion des Pankreas und die Folgen ihres Wegfalles: Ein Fall von fast totaler Agenesie des exokrinen Teiles des Pankreas, Deutsches Arch. f. klin. Med. **173**:339, 1932. Andersen, D. H.: Cystic Fibrosis of the Pancreas, Vitamin A Deficiency, J. Pediat. **15**:763, 1939.

passed through the mouth in infants under 6 months of age and through the nose in older infants and children unless obstruction was encountered. The tube was passed as far as the stomach, the gastric juice was removed and the child was placed on the fluoroscopic table. The tube often bent toward the cardia and then followed the curves of the stomach to the pylorus. If difficulty was encountered it was often possible to direct the tube toward the pylorus by massage of the abdomen. The tube usually passed the pylorus without difficulty, but if it did not the tip was left at the pylorus, with slack tube in the stomach. The infant was then picked up and amused for a few minutes, after which a second inspection usually showed the tube in the duodenum. In preliminary experiments the maximum enzyme potency was found to be at or below the level of the ampulla of Vater, as one would expect. Injection of 5 to 10 cc. of air should produce an air bubble in the duodenum. When the tube was found to be in the correct position, it was held there by a narrow strip of adhesive tape binding the tube to the face. Use of the fluoroscope to determine the position of the tube is essential, since absence of the pancreatic enzymes from gastric juice is not of diagnostic significance. Care should be taken to use the fluoroscope as little as possible, to avoid the hazard of overdosage.

With the tube in place, material was aspirated by gentle suction with a Luer syringe (20 cc.) until a sufficient amount was obtained (6 to 8 cc.); the time required was usually fifteen minutes to one hour. Any change in the appearance of the material was noted; the new material was collected and analyzed separately, and the position of the tube was again checked by fluoroscopic examination. A maximum period of two hours was allowed for the entire procedure, but less than one hour was usually required. Failure to obtain the juice from the appropriate site was experienced in 3 instances in the course of the study: once with a child of 3 months having hypertrophic pyloric stenosis and pancreatic fibrosis, and twice with infants who vomited easily, the tube not being retained long enough for collection of adequate material.

No untoward effects were observed, even in marasmic infants, when the procedure was carried out as described. The importance of previous hydration and of a time limit for the procedure were realized in the case of one of the first patients examined. An inadequate amount of duodenal juice was obtained in a period of four hours, at which time a rise in temperature was noted. The tube was removed and water was given, with a subsequent fall in temperature to normal within two hours. This experience has never been repeated.

The psychic trauma is much less than in adult patients. The younger infants often appear to consider the tube a fair substitute for a meal, but this illusion decreases with age. Older infants object to the passage of the tube, but when it is in place and stationary they are able to forget about it and sleep or play. With children over the age of 2 years cooperation can often be obtained throughout the procedure, and after the tube is in place the patient usually becomes engrossed in the crayons and paint books provided.

Methods of Making Determinations.—The duodenal juice was kept on ice, and the determinations were made on the same day. When material was sent from other cities it was packed in solid carbon dioxide (dry ice), sent by air mail and studied on the day after it was obtained. The assay of enzymes was within the lower range of the figures obtained for infants in the Babies Hospital. In all cases the trypsin was determined as soon as possible, since it was found to decrease more rapidly than the other enzymes on standing.

A necessary part of the equipment was a water bath with a glass front which was kept at a constant temperature of 37.5 C. ± 0.005 degree. For reasons of expediency the same temperature was used for all determinations in the present experiment. Unfortunately the values so obtained are not directly comparable to those given by the original authors of the three methods used, for the tests as described by them were all made at different temperatures. Trypsin and amylase were measured by the viscosimetric method.[6] The substrate for the assay of trypsin was 5 per cent gelatin buffered to a p_H of 7.4 with tenth-molar sodium dihydrogen phosphate-phosphoric acid buffer.[6d] The substrate for the assay of amylase was a 5 per cent starch solution buffered to a p_H of 5.6 with sodium acetate–acetic acid buffer and prepared as described by Thompson, Tenant and Wies [6b] and made up weekly. The procedure has been described by Waksman and Davison.[6d] The duodenal juice was diluted sufficiently so that the viscosity of the 1:10 mixture of diluted juice and substrate decreased 20 per cent in the course of a period ranging from fifteen to ninety minutes. A dilution of 1:50 or 1:100 was usually satisfactory; but if it was not, the determination was repeated with another dilution as suggested by the first experiment. In cases of pancreatic deficiency, either a 1:5 dilution or the undiluted material was used. The dilution should be made immediately before it is to be used, as the potency of the enzymes decreases rapidly after dilution with distilled water. The viscosity of the diluted material introduces a negligible error, but when undiluted or a dilution under 1:10 or serum is used there is a variable degree of error.

The serum amylase was determined in the same manner as the duodenal juice amylase, undiluted serum obtained while the patient was fasting being used. The calculations were based on the time of flow at zero time as determined by control tests with a 1:10 mixture of distilled water and substrate except when serum or undiluted duodenal juice was used. Under such circumstances the time of flow at the first reading was used as a base line. Since the decrease in viscosity was always gradual under these circumstances, the error introduced was low, being estimated at well under 5 per cent. One unit was defined as the amount of enzyme required to decrease the viscosity of the mixture 20 per cent in 1 hour, and calculations were made as described by Waksman and Davison.[7] All determinations were made in duplicate.

The lipase was determined by the Willstätter titration method.[8] One cubic centimeter of duodenal juice was diluted up to 10 cc. with distilled water and

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6. (*a*) Northrop, J. H., and Hussey, R. G.: A Method for the Quantitative Determination of Trypsin and Pepsin, J. Gen. Physiol. **5**:353, 1923. (*b*) Thompson, W. R.; Tenant, R., and Wies, C. H.: Studies in Starch Amylase Viscosimetry: I. A Sensitive Precision Method for the Estimation of Amylolytic Activity Applicable to Human Serum, J. Biol. Chem. **108**:85, 1934. (*c*) Davison, W. C.: A Viscosimetric Method for the Quantitative Determination of Amylase, Bull. Johns Hopkins Hosp. **37**:281, 1925. (*d*) Waksman, S. A., and Davison, W. C.: Enzymes, Baltimore, Williams & Wilkins Company, 1926. (*e*) Thompson, W. R.; Johnson, C. E., and Hussey, R.: A Viscosimetric Method of Estimating Enzyme Concentration with Special Reference to Amylase, J. Gen. Physiol. **15**:1, 1931.

7. Waksman and Davison,[6d] p. 11.

8. Willstätter, R.; Waldschmidt-Leitz, E., and Memmen, F.: Bestimmung der pankreatischen Fettspaltung, Ztschr. f. physiol. Chem. **125**:93, 1923.

poured into a 50 cc. Erlenmeyer flask containing 2.6 cc. of olive oil. To this were added 2 cc. of buffer consisting of a 1:2 mixture of normal ammonium hydroxide and normal ammonium chloride; 0.5 cc. of 2 per cent calcium chloride and 0.5 cc. of a fresh solution of 3 per cent egg albumin. The flask was stoppered, shaken hard for several minutes and placed in a water bath at 37.5 C. The determination was made in duplicate except in a few instances in which the quantity of juice was inadequate. Two control tests were made, with 10 cc. of distilled water used, in place of diluted juice. The flasks were made up at intervals of three to five minutes, to allow time for titration after incubation for one hour ± one minute. After incubation the contents of each flask were emptied into a wide-mouthed 250 cc. Erlenmeyer flask containing 12 drops of a saturated alcoholic solution of cresolphthalein as indicator. The small flask was then rinsed twice with ether (a total of 20 cc.) and twice with 95 per cent alcohol. Approximately 100 cc. of alcohol was added to the titration flask and the mixture titrated with tenth-normal alcoholic potassium hydroxide. A lipase unit has been defined by Willstätter as the amount of lipase which under these circumstances will split 24 per cent of the olive oil. This figure was calculated as follows:

$$\frac{\text{Cc. of N/10 KOH} \times \text{factor of KOH}}{20.7} \times 100 = \text{units/100 cc.}$$

This method is less satisfactory than the viscosimetric methods used for the amylase and trypsin, because of variations in the olive oil and in the emulsification of the incubation mixture.

The stool fat was determined by the following means: The patient was placed on a known and constant diet for twenty-four or forty-eight hours before the beginning of the collection of stools. The longer period was used for infants over 8 months of age. For young infants the diet was composed of evaporated milk and cane sugar or corn syrup (Karo); for older infants a normal infant's diet was given; for both groups the caloric value approximated 110 calories per kilogram. The stools were then collected for forty-eight to seventy-two hours, being kept in a closed glass container in the ice box. When the collection was complete, the container was weighed and the contents were mixed well. An aliquot of 2 to 3 Gm. wet weight was dried to constant weight. Another aliquot of about 50 Gm. of stool, acidified with a few drops of concentrated sulfuric acid, was mixed with an approximately equal volume of anhydrous sodium sulfate in a 400 cc. beaker. This mixture was transferred quantitatively with ethyl oxide (ethyl ether) to a muslin bag of an extraction apparatus of the type described by Sperry,[9] by means of a 1 liter round-bottomed flask and a 1 pint (470 cc.) percolator. Heat was supplied by a 40 watt mazda bulb surrounded by a tin can. A coil of ¼ inch (0.6 cm.) copper tubing was placed in and above the upper part of the percolator, and through it ran a stream of cold water. The stool was subjected to continuous extraction with ethyl oxide for four hours and then removed and ground to a powder in a large mortar. Extraction was then repeated for another four hours. The ethyl oxide extract was then transferred to a 500 cc. separatory funnel, washed three times with water, extracted three times with fifth-normal sodium hydroxide and washed three times with water. The alkaline extracts were each

9. Sperry, W. M.: Lipid Excretion: III. Further Studies of the Quantitative Relations of the Fecal Lipids, J. Biol. Chem. **68**:357, 1926.

transferred directly to a second separatory funnel, acidified with an excess of twice-normal sulfuric acid and shaken up with ether. The aqueous layer was discarded. The ether in the first funnel therefore contained the neutral fat and nonsaponifiable material, and that in the second funnel contained the fatty acids. These fractions were then transferred to tared 100 cc. beakers; the ether was evaporated off and the sediment dried to constant weight. The sum of the contents of both beakers gives the total ether-soluble lipids (referred to as "total fat"). No attempt was made to separate the neutral fat and nonsaponifiable material. The neutral fat, fatty acids and total fat were then calculated in terms of the dried weight of the stool.

Selection of Patients.—All patients were between the ages of 2 weeks and 5 years, with the exception of a child with pancreatic deficiency who was 7½ years old. Five groups of subjects are included in the present report: (1) 53 normal infants and children; (2) 25 infants and children with chronic diarrhea; (3) 3 infants with the classic picture of celiac disease; (4) 3 infants with extreme marasmus; (5) 15 infants with congenital pancreatic deficiency. One infant is included in both the group with the celiac disease and the marasmic group. The study therefore includes observations on 98 infants and children.

The patients in the control group were selected by the following criteria: All were of normal weight and physical development for their age and were gaining at the time of the examination. No children were included who had a history of repeated or prolonged attacks of diarrhea or of other gastrointestinal or nutritional difficulties at any time. The hospital diagnosis in most cases was one of the following: acute pneumonia, recovered; mental deficiency; lesion of the central nervous system; benign tumor (i. e., hemangioma); congenital heart disease without decompensation; infection of the urinary tract (recovered). Several entirely normal infants were included.

The group with diarrhea was composed of infants and children who gave a history of repeated or prolonged attacks of diarrhea, the latest within two months of the time of examination. In most instances the diagnosis was "diarrhea due to parenteral injection," but for 5 of the 6 to 12 month group and for all of those over 1 year of age the diagnosis of celiac disease had been suggested by one or more observers at some time. No children known to be infected with organisms of the dysentery group and none with only a single attack of acute diarrhea are included in this group. All patients were afebrile at the time of the examination, but in some the weight was stationary or decreasing. No patients presenting the classic picture of idiopathic steatorrhea are included in the group. Chemical analysis of the stool for fat was made in 8 of the 10 cases in which the patient was over the age of 1 year; with a normal diet the fat formed from 10 to 22 per cent of the dried weight of the stool. For a similar number of controls the range was from 10 to 26 per cent; hence these figures are within normal limits. Undigested starch granules were found in the stools of many of the children in the two older groups.

Three patients with classic idiopathic steatorrhea were observed, 1 of which is listed in the group with marasmus. An elevated fat content of the stool with a normal diet was required for this diagnosis. Three patients with marasmus not included in the group with diarrhea are reported on. All 3 patients were thought to have cystic fibrosis of the pancreas because of the extreme inanition and pro-

longed diarrhea. The initial examination was made for purposes of diagnosis, and after clinical improvement a subsequent examination was made to eliminate finally the possibility of pancreatic disease.

Fifteen patients with congenital pancreatic deficiency are reported on. Seven of these are from the Babies Hospital; for the data on the remainder I am indebted to Doctors Blackfan, May and McCreary of the Boston Children's Hospital, Dr. Levine of the New York Hospital, Dr. Powers of the New Haven Hospital and Dr. Monfort of the Norwegian Hospital of Brooklyn, who provided not only material for study but records of the subsequent course and gave me permission to publish the pertinent data. Ten of these 15 patients died within a year of the time of examination, all with symptoms characteristic of the disease. Postmortem examination was made in 5 cases, and cystic fibrosis of the pancreas was found in all. In 1 case no record of the later history has been obtained. Four children are living; 2 of these are doing well under careful treatment and the other 2 are doing fairly well but have symptoms of chronic infection of the respiratory tract.

TABLE 1.—*Pancreatic Enzymes in Duodenal Juice*

Age	No.	Trypsin Units per Cc. Mean	Trypsin Units per Cc. S. D.	Amylase Units per Cc. Mean	Amylase Units per Cc. S. D.	Lipase Units per 100 Cc. Mean	Lipase Units per 100 Cc. S. D.
Controls							
0- 2 mo.	10	137.6	125.6	4.3	3.9	21.2	10.4
2- 6 mo.	11	138.8	98.1	25.3	23.1	26.6	21.2
6-12 mo.	11	250.5	211.5	113.9	63.3	34.6	27.6
1- 2 yr.	9	262.0	263.0	177.4	207.5	18.8	11.1
2- 5 yr.	13	195.0	106.8	243.9	249.0	19.6	12.8
Diarrhea							
2- 6 mo.	8	161.2	88.7	9.4	9.5	25.5	20.5
6-12 mo.	7	151.0	23.4	48.2	64.9	28.7	21.0
1- 5 yr.	10	188.6	230.1	61.8	39.5	20.0	8.7

RESULTS

Normal Subjects.—When the sources of error in the method of collecting the duodenal juice are considered, it is surprising to find the concentrations of the pancreatic enzymes no more variable than they are. Much of the variation results from the dilution of the juice with unknown amounts of gastric juice, bile and succus entericus, all of which tend to lower the figures; hence the higher figures obtained probably approximate the true concentration of the enzymes in the pancreatic secretion. A concentration of less than 100 units of trypsin per cubic centimeter was not often encountered, and all figures above this are therefore considered normal for practical purposes. The concentration of trypsin and of lipase does not vary greatly with age (table 1; charts 1 and 2). Amylase, however, is present in only small amounts and is often absent in infants under the age of 3 months (table 1; chart 3). Between the ages of 3 and 6 months there is a rapid increase, which becomes more gradual in the second half of the first year. Maximal figures are reached at about

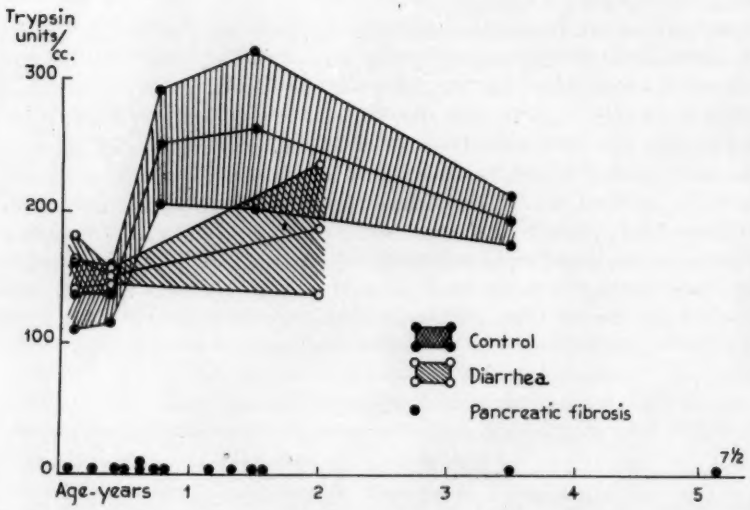

Chart 1.—Comparison of concentrations of trypsin in the duodenal juice of normal children, of children with pancreatic fibrosis and of children with prolonged diarrhea.

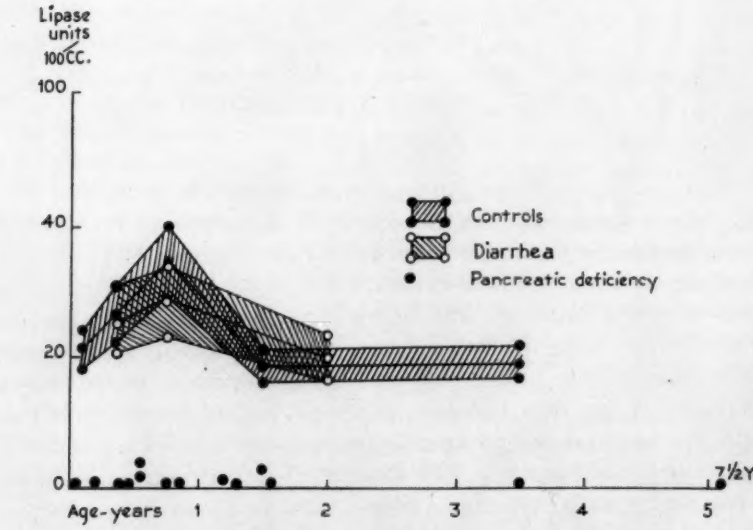

Chart 2.—Comparison of concentrations of lipase in the duodenal juice of normal children, of children with pancreatic fibrosis and of children with prolonged diarrhea.

the third year. This confirms the findings of Klumpp and Neale [4] and extends their observations to younger children. It would seem that the infant is not prepared to digest much starch before the third or fourth month.

Patients with Chronic Diarrhea.—In this group the concentration of amylase is significantly lower than normal after the age of 6 months (chart 3; tables 1, 2 and 3). No significant differences are found in the levels of trypsin and lipase (charts 1 and 2).

Patients with Idiopathic Steatorrhea.—Three children who presented the classic picture of idiopathic steatorrhea with an excess of fat in the

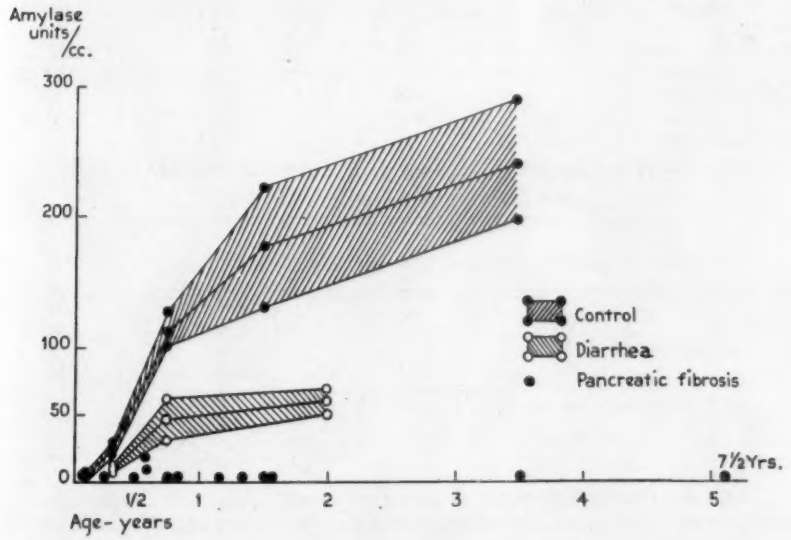

Chart 3.—Comparison of concentrations of amylase in the duodenal juice of normal children, of children with pancreatic fibrosis and of children with prolonged diarrhea.

stools showed normal amounts of pancreatic enzymes in the duodenal juice (table 4).

Marasmic patients.—Three infants who presented the clinical picture of marasmus, with loose, dry skin, persistent diarrhea, muscular atrophy, severe loss of weight and inanition, showed a definite depression of the level of all three enzymes (table 5). The stools of 2 of them were analyzed for fat, and an abnormally high amount was found. All 3 infants responded well to therapy, and all showed enzyme concentrations within the normal range after clinical improvement.

Patients with Pancreatic Deficiency.—Fifteen patients presenting the clinical picture of pancreatic deficiency showed minimal amounts of pancreatic enzymes in the duodenal juice (table 6; charts 1 and 2). No appreciable amounts of trypsin were present at any time. Small amounts of lipase and variable amounts of amylase were sometimes present. The

TABLE 2.—*Comparison of Amylase in Control Infants and in Infants with Diarrhea, Age 6 to 12 Months*

	Amylase Level		
	Below 50 Units	Above 50 Units	Total
Control	1 (1.5)	10 (9.5)	11
Diarrhea	6 (5.5)	1 (1.5)	7
Total	7	11	18

χ^2=7.93.
P =<.01.

TABLE 3.—χ^2 *in Comparison of Amylase in Control Infants and in Infants with Diarrhea in Three Age Groups*

Group	Age	χ^2
1	2- 6 months	0.72
2	6-12 months	7.93
3	1- 5 years	2.63
		11.28

1+2+3 P=between .02 and .01
2+3 P= <.01

TABLE 4.—*Duodenal Enzymes in Two Patients with Idiopathic Steatorrhea*

	Age	Enzymes			Stool fat, per Cent Dried Wt.
		T.	A.	L.	
J. B.	16 mo.	185.0	156.0	20.8	30.6
A. G.	3 yr.	220.8	364.0	18.0	44.2
	3 4/12 yr.	154.0	228.0	19.2	24.1
Normal	1-2 yr.	262.0	177.4	18.8	10.7-25.6
Diarrhea	1-2 yr.	188.6	61.8	20.0	10.8-21.6

amylase was found only in cases in which there was a productive cough and in which small masses of mucus were present in the duodenal juice. It seems probable that the amylase originated in the salivary glands rather than in the pancreas and survived passage through the stomach because of either low gastric acidity or the protection of the mucus or both.

Determination of Serum Amylase in Several Groups.—The serum amylase was determined in 62 control infants and children, in 14 infants

and children with chronic diarrhea and in 11 with pancreatic deficiency. The duodenal juice was assayed for amylase within a few days of the determination of serum amylase in the cases of 36 control subjects and of all the patients with diarrhea or pancreatic deficiency; it was hoped that the determination of serum amylase might prove of diagnostic value in cases of congenital pancreatic deficiency. However, the value for

TABLE 5.—*Duodenal Enzymes in Patients with Marasmus from Prolonged Diarrhea, During Illness and After Recovery*

	Age, Months	Weight, Kg.	T.	A.	L.	Condition
L. M.	7	5.56	46	29	16	Marasmic
	8	6.25	77	20	94	Mod. improved
	9½	8.13	145	58	37	Much improved
H. R.	18	8.6	33	14	16	Marasmic
	19	8.7	532	109	27	Mod. improved
M. G.	2	3.57	24	3	10	Marasmic
	4	4.90	307	119	21	Much improved
Fibrosis of Pancreas						
Maximum values			6	44	4	

TABLE 6.—*Duodenal Enzymes in Patients with Pancreatic Fibrosis**

	Age	T.	A.	L.		
W. A.	1 mo.	1	0	0	?	Boston
G. D.	3 mo.	0	0	1	O. K. at 2 yr.	Babies Hosp.
D'A.	5 mo.	0	44	0	P. M.	Boston
D'A.	6 mo.	0	0	0	Living	New Haven
W. C.	7 mo.	6	16	4	Died; no P. M.	Babies Hosp.
F. D.	7 mo.	2	1	2	Died; no P. M.	Babies Hosp.
T. L.	9 mo.	0	1	0	Died; no P. M.	Cornell
A.	10 mo.	0	0	0	P. M.	Boston
S. K.	14 mo.	0	3	1	P. M.	Babies Hosp.
C. J.	16 mo.	0	0	0	O. K. at 2½ yr.	Babies Hosp.
P. D.	18 mo.	0	0	3	P. M.	Boston
C. G.	19 mo.	0	0	0	Died; no P. M.	Babies Hosp.
J. G.	2½ yr.	1	0	0	Died; no P. M.	Babies Hosp.
R. E.	7½ yr.	2	0	0	Living	Babies Hosp.
T.	?	10	0	4	P. M.	Boston

* 15 patients: 4 living; 1 no record; 10 died; 5 autopsies.

serum amylase of the patients with pancreatic deficiency fall within the range of the control figures (chart 4). In the control group there is a correlation between the serum amylase and the duodenal juice amylase. Eleven subjects had an amylase content of the duodenal juice of less than 10 units per cubic centimeter, and 8 of these had a serum amylase concentration of less than 0.02 unit per cubic centimeter, the highest figure being 0.18 unit. Of the remaining 25 children there was only 1 with a serum amylase value below 0.02 unit per cubic centimeter. The

majority (15 subjects) had a figure between 0.08 and 0.20 unit, the highest level being 0.36 unit. On studying the data one gains the impression that when the duodenal amylase is below the level of about 10 units per cubic centimeter little or no amylase is found in the blood; when the duodenal amylase is above that level amylase is present in the serum in about the same concentration, regardless of the assay of amylase in the duodenal juice. Since the lower figures for both duodenal and serum amylase were obtained from the younger infants, they may also be interpreted as a function of age.

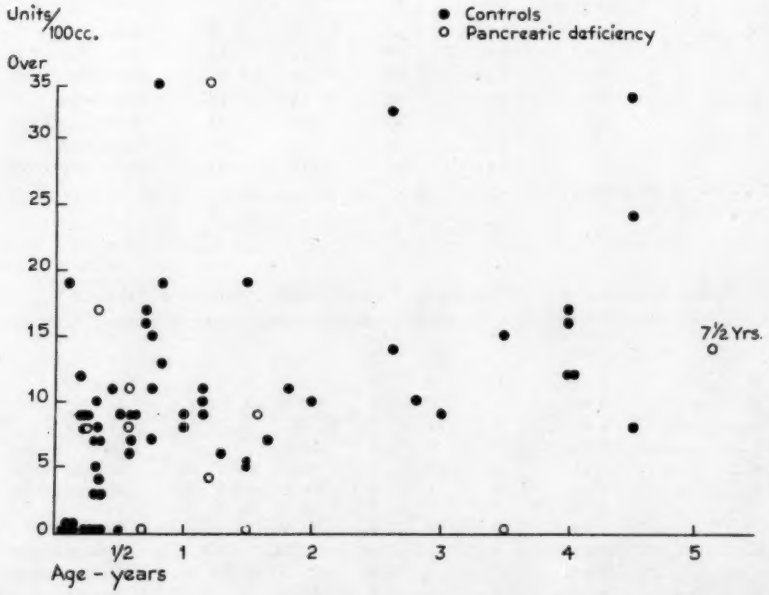

Chart 4.—Concentration of amylase in the serum of normal children and of children with pancreatic deficiency.

COMMENT

Diagnosis of Cystic Fibrosis of the Pancreas.—The determination of the levels of pancreatic enzymes in the duodenal juice provides a reliable means of diagnosis of cystic fibrosis of the pancreas if certain sources of error are kept in mind. The chief of these is the possibility that the material studied was not obtained from the middle third of the duodenum. It is therefore essential to ascertain the position of the tube by means of the fluoroscope. The enzymes are absent, or present in only small concentrations, in the stomach, in the first few centimeters of the duodenum and in the jejunum in normal persons. If appreciable quantities

of enzymes are demonstrated in the duodenal juice, the diagnosis of pancreatic deficiency may be considered disproved. If no enzymes are present in the duodenal juice on one occasion it is wise to repeat the examination on another day for confirmation.

The second precaution necessary is to rely primarily on the assay of trypsin in differential diagnosis. The amylase content is normally low in early infancy and may be extremely low in the presence of chronic diarrhea without pancreatic fibrosis. Moreover, the swallowing of saliva, especially when gastric acidity is low, may produce deceptive results in cases of pancreatic deficiency. The assay of lipase is less reliable than that of the other two enzymes for technical reasons. Moreover, low lipase figures have been obtained for a number of patients not included in the series reported here (i. e., patients with atresia of the common duct). In no instance in our experience has trypsin been absent from the duodenal juice of an infant or child without pancreatic deficiency. The low values found in association with extreme marasmus are above any found in cases of pancreatic fibrosis, but a second determination after clinical improvement is reassuring. Assay of trypsin in the duodenal juice is therefore a reliable means of diagnosis of pancreatic deficiency.

Differential Diagnosis of the Celiac Syndrome Without Congenital Pancreatic Deficiency.—Observations on this syndrome are reported at this time primarily for comparison with those on pancreatic fibrosis. The following remarks may be considered as a preliminary note on work still in progress, and as tentative rather than conclusive.

The term celiac disease has been used in a large group of cases of chronic indigestion in children characterized by large abnormal stools containing undigested material. It is by no means certain that all the conditions to which the term is applied are on the same functional basis. Digestion is a complicated process, and so also is the absorption of the products of digestion. Failure in either digestion or absorption of fat, protein or carbohydrate or any combination of these might be expected to produce a symptom complex similar to that described as celiac disease. Perusal of the literature on celiac disease with this concept in mind convinces one that not all cases are alike and also that the fundamental nature of the difficulty in digestion has been infrequently and inadequately sought for. Much of the European literature lays emphasis on the difficulty in digestion of fat, and good evidence for an excess of fat in the stool is offered in many of the reported cases. In American literature the difficulty in carbohydrate digestion first emphasized by Howland [10] is in the foreground. Evidence for this view is found in the presence of undigested starch in the stools and in the ability of many of

10. Howland, J.: Prolonged Intolerance to Carbohydrates, Tr. Am. Pediat. Soc. **33**:11, 1921.

the infants with celiac disease to tolerate fat in the diet if the carbohydrate is low. The alterations in fecal bacterial flora have been interpreted as secondary to changes in the character of the stools. The criteria for the diagnosis of celiac disease have also varied, and the apparent incidence of the disease has differed in various clinics as a consequence. If inability to tolerate a normal diet is considered diagnostic, the disease is a fairly common one; but if an excess of fat in the stools is required for diagnosis, only a few cases are encountered in the larger clinics annually. The more reliable methods of measuring stool fat are slow and expensive, and in most cases of the celiac syndrome the analysis is not made. Clinical experience has led to a rough division of patients with the celiac syndrome into two groups: the larger number while on a normal diet have abnormal stools containing starch granules but show a fair gain in weight; there is also a tendency to exacerbations, especially during the rather frequent infections of the upper respiratory tract. Every experienced pediatrician has seen patients with these symptoms. They have been called "near-celiacs," "celiacs" or "mild celiacs," and they are generally believed to have mild examples of the more severe variety of classic celiac disease. The second group is composed of a smaller number of children with a more severe disease picture, with loss of weight, sometimes leading to marasmus and often requiring prolonged hospitalization. These are the patients with classic idiopathic steatorrhea, with demonstrable increase in stool fat. Their cases form the bulk of those reported, especially in the European literature. Both groups respond to the high protein, low fat, low carbohydrate diet usually given for celiac disease, and in both groups the tolerance to a normal diet is recovered only after prolonged treatment, usually measured in years.

In the present series of children with chronic diarrhea, 5 of the 7 patients between the ages of 6 and 12 months and all of the 10 patients over the age of 1 year were considered by one or more observers to be possibly suffering from early celiac disease. A fat analysis of the stool was made for 10 of the 15 patients while they were on a normal diet, and the fat content was within the normal range in all instances. The stools of most of these patients showed great numbers of starch granules on microscopic examination, and their duodenal juice contained less amylase than was found in that of the control group. The repeated association of low duodenal juice amylase, bulky stools with an excess of starch granules but no excess of fat, and chronic diarrhea would seem to be more than coincidence. This impression has been strengthened recently by clinical experience with several children who had made no progress on a low fat, high starch diet but responded promptly to a starch-free diet containing a normal amount of fat, some sugar and a high level of protein.

Not all of the patients included in the group with chronic diarrhea had a low amylase content in the duodenal juice, and in many cases the examination of the stool was inadequate. The borderline between chronic diarrhea with starch intolerance and that due to parenteral injection is vague, and no attempt has been made to separate the two types in the present paper. Further study is required before the syndrome of starch intolerance can be clearly delineated. The present report merely gives evidence of the existence of such a syndrome as distinct from both idiopathic and pancreatic steatorrhea.

In the three years covered by this study only 3 patients with classic celiac disease have been encountered in the Babies Hospital. All 3 had a high fat content of the stool (31, 37 and 44 per cent of dry weight respectively) on a normal diet, normal levels of pancreatic enzymes in the duodenal juice (except during a period of marasmus in 1 patient), intolerance to dietary fat and a prolonged severe course with eventual response to therapy. The difficulty in fat digestion was apparently not in the splitting of fat, since lipase was present in normal amounts and the stool fat was chiefly in the form of fatty acids (78, 80 and 81.5 per cent). The observations in these cases appear to conform to the hypothesis of an essential failure in fat absorption. Quantitative studies on the excretion of carbohydrates have not been made as yet.

On the basis of these observations it is suggested that two further groups of patients in addition to those with pancreatic fibrosis be tentatively separated from the patients presenting the celiac syndrome, with full realization that our knowledge is incomplete and that further groups may be distinguished. These two groups are (1) patients with "near-celiac" disease, who have starch intolerance with a low concentration of amylase, undigested starch in the stools and dietary intolerance to starch but not to fat; and (2) patients with classic idiopathic steatorrhea with normal amounts of duodenal enzymes (in the few cases so far studied) and with intolerance to dietary fat, apparently because of failure of absorption. The evidence presented here makes it unlikely that the latter group has a severe degree of the disability shown by the former.

Diagnosis of Functional Pancreatic Insufficiency in Marasmus.—Functional pancreatic insufficiency in marasmus is suggested by observations on 3 patients. All of them had decided depression of the level of all the enzymes when the marasmus was severe, with restoration of normal concentrations after clinical improvement. It seems probable that the depression of pancreatic activity is secondary to the marasmus and is a specific example of the decreased activity of various organs in inanition. Confirmation of the view that the depression of function is actually present is given by the increased volume of the stools and the presence of a high percentage of fat in them. This functional pancreatic deficiency may well contribute a component to the clinical picture. More

observations over a longer period are required before further conclusions can be drawn. One of these patients presented the clinical picture of idiopathic steatorrhea both before and after the period of inanition, and the relationship of these two phenomena remains to be investigated.

SUMMARY AND CONCLUSIONS

1. The assay of trypsin in the duodenal juice is a reliable means of diagnosis of pancreatic deficiency. Trypsin is uniformly present in normal amounts in the duodenal juice of patients with other varieties of the celiac syndrome and of normal infants. It is present in smaller but appreciable amounts in the presence of extreme marasmus and is uniformly low or absent with congenital pancreatic deficiency.

2. The assay of amylase is not a reliable means of diagnosis, because of its low concentration during the first months of life in normal infants and in many older infants and young children with chronic diarrhea. Amylase may occasionally be present in patients with pancreatic fibrosis, presumably because of the failure of salivary amylase to be destroyed in passing through the stomach.

3. Lipase is present in normal infants of all ages. The concentration is reduced in congenital pancreatic deficiency, but the assay is less reliable for diagnosis because of low values in occasional control cases and because of technical difficulties.

4. Determination of serum amylase is of no value in the diagnosis of congenital pancreatic deficiency.

5. It is suggested that two further groups of patients be separated from the general group with celiac disease. These are: (1) patients with "near-celiac" disease, who show intolerance to starch in the diet, a low level of amylase in the duodenal juice, starch in the stools but no excess of stool fat and a relatively mild though prolonged clinical course; (2) patients with classic idiopathic steatorrhea, with intolerance to fat, a high concentration of stool fat, normal amounts of pancreatic enzymes and a severe and protracted clinical course. The evidence at hand suggests that the difficulty lies in the absorption rather than in the digestion of fat. Further groups may remain to be discovered among the patients presenting the celiac syndrome.

6. In 3 patients with severe marasmus the trypsin, amylase and lipase levels were all depressed but returned to normal with clinical improvement. This depression of pancreatic function probably represented merely a specific example of the depression of function of the organism as a whole, but it may well contribute a component to the clinical picture because of consequent difficulties in digestion. The increase in bulk and the excess of fat in the stools of 2 of these infants lend support to this view.

Mrs. Helen S. Kennedy and Mrs. Marialuise Early gave technical assistance.

STUDIES ON COLLOIDAL SULFUR–POLYSULFIDE MIXTURE

IV. A THERAPEUTIC TEST IN RHEUMATIC FEVER

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Acute rheumatic fever and rheumatoid arthritis are treated as distinct clinical entities in most medical treatises. However, certain authoritative sources [1] report the relationship of the two conditions to be more intimate than is commonly supposed. Both rheumatic fever and rheumatoid arthritis are most commonly found in the temperate zones and particularly in a damp environment; in both diseases there is an increased blood sedimentation rate when the infectious process is active, and the acute manifestations of both diseases are modified or controlled by salicylates. It is apparent that no accurate parallel between rheumatic fever and rheumatoid arthritis can be established until full information is available regarding their causation and pathogenesis. Many forms of therapy have been suggested for both conditions, and these are all empiric, palliative and nonspecific.

A large number of patients with arthritis, both rheumatoid and hypertrophic, have allegedly been successfully treated with colloidal sulfur.[2] It has been injected intravenously and intramuscularly in

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1. Pemberton, R.: Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, 1935. Gibson, S.: Rheumatic Fever and Chorea, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 2, chap. 19.

2. (*a*) Massolongo, R., and Vivaldi, S.: Riforma med. **32**:781, 1916. (*b*) Comrie, J. D.: Lancet **1**:991, 1917. (*c*) Secor, W. L.: M. Rec. **94**:765, 1918. (*d*) Meyer-Bisch, R.: München. med. Wchnschr. **68**:516, 1921. (*e*) Meyer-Bisch, R.: Klin. Wchnschr. **1**:575, 1922. (*f*) Monaghan, W. J., and Garai, F.: M. J. & Rec. **120**:24 and 75, 1924. (*g*) Dengler, J.: Klin. Wchnschr. **3**:316, 1924. (*h*) Reimann, H. A., and Pucher, G. W.: Am. J. M. Sc. **168**:77, 1924. (*i*) Dollinger, B.: Wien. klin. Wchnschr. **38**:1260, 1925. (*j*) Weicksel, J.: Ztschr. f. klin. Med. **103**:794, 1926. (*k*) Cawadias, A. P.: Lancet **1**:1283, 1927. (*l*) Loeper, M.: Schweiz. med. Wchnschr. **15**:1122, 1934. (*m*) Loeper, M.; Lesure, A., and Tonnet, J.: Compt. rend. Soc. de biol. **116**:31, 1934. (*n*) Sullivan, M. X.:

(Footnote continued on next page)

aqueous solution, injected intramuscularly in oil solution and used in baths and orally. Attempts have been made to rationalize its use on the basis of the existence in the arthritic person of a defective systemic sulfur metabolism,[2k] a faulty sulfur metabolism of the articular cartilages [2m, n] or a disturbed deposition of cystine,[2n-u] all of which are stated to be remedied by administration of sulfur. Claims of the value of the treatment have ranged from favorable to extravagant. From other sources [3] has come unfavorable mention of the use of colloidal sulfur. Freyberg, Block and Fromer [4] studied the sulfur metabolism in normal and in arthritic subjects when colloidal sulfur was given intravenously, intramuscularly and orally. They found no differences in the sulfur metabolism of the normal and of the arthritic subjects or any alterations in the cystine content of the finger nails after treatment with sulfur, and they concluded that in the absence of demonstrable sulfur deficiency no need for sulfur exists in persons with arthritis.

It is clear from the conflicting evidence at hand that no definite proof or disproof of the therapeutic value of colloidal sulfur has thus far been advanced. The obscure causation of rheumatism and its chronic nature, with frequent exacerbations and remissions, make it difficult to evaluate the response to any new form of therapy unless the therapy should happen to prove dramatically specific. Undoubtedly, the improvement with any type of experimental regimen is due in many instances to the existence of more desirable hygiene and habits of the patient during the period of observation. Thus it is essential in investigating the therapeutic efficacy of sulfur to compare the clinical course of the patients undergoing treatment with that of a series of control patients under identical management except for the omission of sulfur.

M. Ann. District of Columbia **3**:233, 1934. (*o*) Sullivan, M. X., and Hess, W. C.: J. Bone & Joint Surg. **16**:185, 1934. (*p*) Argy, W. P.: ibid. **16**: 909, 1934. (*q*) Rawls, W. B.; Gruskin, B. J., and Ressa, A. A.: Am. J. M. Sc. **190**:400, 1935. (*r*) Wheeldon, T.: J. Bone & Joint Surg. **17**:693, 1935. (*s*) Woldenberg, S. C.: M. Rec. **139**:161, 1934; (*t*) M. Bull. Vet. Admin. **12**:10, 1935; (*u*) South. M. J. **28**:875, 1935. (*v*) Senturia, B. D.: J. Bone & Joint Surg. **16**:119, 1934; (*w*) J. Lab. & Clin. Med. **20**:855, 1935. (*x*) Sashin, D., and Spanboch, J.: M. Rec. **142**:332, 1935. (*y*) Krestin, D.: Brit. M. J. **2**:1144, 1935. (*z*) Clark, M. M.: New York State J. Med. **37**:569, 1937. (*a'*) Johnson, P. T.: Clin. Med. & Surg. **43**:332, 1936. (*b'*) Rödel, W.: Klin. Wchnschr. **8**:94, 1929. (*c'*) Parmenter, D. C.: Kentucky M. J. **35**:14, 1937.

3. Cecil, R. L.: Medical Treatment of Chronic Arthritis, J. A. M. A. **103**: 1583 (Nov. 24) 1934. Kinsella, R. A.: Radiology **24**:413, 1935. Holbrook, W. P., and Hill, D. F.: Treatment of Atrophic Arthritis, J. A. M. A. **107**:34 (July 4) 1936. Colloidal Sulfur in the Treatment of Chronic Arthritis, report of the Council on Pharmacy and Chemistry, J. A. M. A. **111**:1657 (Oct. 29) 1938. Hench, P. S., and others: Ann. Int. Med. **13**:1864, 1940. Abrams, N. R., and Bauer, W.: New England J. Med. **222**:541, 1940.

4. Freyberg, R. H.; Block, W. D., and Fromer, M. F.: J. Clin. Investigation **19**:433, 1940.

Such a study has never heretofore been made. The low cystine concentration in the tissues reported to obtain in most arthritic persons has been attributed either to a metabolic defect resulting in faulty synthesis or deposition of this amino acid or to an excessive formation of toxic products which are excreted as ethereal sulfates and thus deplete the organism of sulfur from what is presumably the most readily available source. However, it has been repeatedly pointed out that the sulfur partition is normal in the urine of persons with arthritis.[5] Furthermore, the logical procedure to supplement a cystine deficiency is the administration of a high protein diet or of cystine itself.

No trial of the use of colloidal sulfur in the treatment of children suffering from acute rheumatic fever has ever been made. Since it is not unlikely that acute rheumatic fever and rheumatoid arthritis are related or even identical conditions, and since we had at our disposal a group of rheumatic children hospitalized under constant and rigid supervision, we felt that a controlled therapeutic test of colloidal sulfur on such children would be illuminating in evaluating the efficacy of this form of treatment.

MATERIAL AND METHOD OF STUDY

For our investigations we used a colloidal sulfur–polysulfide preparation whose pharmacologic and metabolic behavior was known to us from previous studies.[6] This is a concentrate of a natural sulfur spring water containing 5 per cent colloidal and polysulfide sulfur (doses are stated in milligrams of this component). It was found to be highly toxic when given parenterally, causing extensive damage to the parenchyma of the lungs; when given orally in any reasonable dose to animals or human beings it was harmless. When ingested by the human subject in amounts up to 12 mg. per kilogram of body weight it was completely absorbed, oxidized and excreted in toto as urinary inorganic sulfate within sixteen hours. These observations indicated to us that in order to give patients adequate amounts of sulfur and to be certain that any effect was that of sulfur itself, oral administration was the procedure of choice.

The children from whom the patients for study were selected received the routine treatment which has been successfully employed over a period of years, consisting essentially of proper diet and rest, a well ordered way of living and treatment of emergencies when these arise. The criteria of improvement in such patients have been based on (*a*) disappearance of activity of the infection as reflected in a return of the blood sedimentation rate to normal, (*b*) establishment of compensation for the cardiac lesions as determined by physical examination, and (*c*) general increase in weight and strength. Patients with high sedimentation rates were selected and were given 250 mg. of the colloidal sulfur daily in 10 per cent solution, which was placed in paraffin-coated capsules because of its unpleasant odor and taste. At the same time a control group of patients was followed, most of whom were given empty capsules in order to eliminate any possible psychotherapeutic effect of a departure from the usual regimen.

5. Senturia.[2w] Freyberg, Block and Fromer.[4]

6. Greengard, H., and Woolley, J. R.: J. Am. Pharm. A. **29**:289, 1940; J. Biol. Chem. **132**:83, 1940.

The following laboratory procedures were done routinely: 1. The sedimentation rate of the blood was determined weekly, and determinations of hemoglobin and red, white and differential cell counts were made at intervals of two weeks.

TABLE 1.—*Data on Treated Patients*

Patient	Activity			Class ‡		Weight			Duration, Weeks		Cystine, per Cent		
	Admission	Discharge	Localization	Admission	Discharge	Admission	Discharge	Ideal	Total	After Rx	Initial	Final	Previous Attacks
N. R.	+	—	Card.*	2A	1	106	118	89	18	2	8.3	13.2	1
P. M. A.	+	—	Card.	2B	2A	47	63	52	23	9	11.5	11.4	2
L. Fr.	+	+	Card.	2B	2B	52	77	60	Per.‖	Per.‖	9.9	10.3	1
J. Co.	—	—	Chor.†	2A	1	77	93	80	8	—¶	11.3	12.0	0
J. Ca.	+	—	Card.	2B	2A	77	90	85	32	7	9.8	13.7	0
C. E.	+	—	Card.	2B	2A	85	115	108	9	—¶	8.3	13.1	0
T. M.	+	—	Card.	2B	2A	71	92	73	44	13	11.6	11.5	2
L. L.	+	—	Card. chor.	2A	1	58	70	61	16	1	10.4	12.7	1
A. S.	+	—	Card.	2B	2A	74	92	75	16	1	11.1	13.1	1
E. M.	+	+	Card.	2B	2B	65	81	78	Per.	Per.	13.4	13.3	1
L. S.	+	—	Card. chor.	2B	2A	50	50	55	19	7	12.0	12.2	2
J. S.	+	?	Card.	—§	—§	79	93	81	13	4	11.8	11.3	0
N. D.	+	—	Card.	2B	2A	45	51	47	?	2	8.5	10.7	?
V. L.	+	—	Card.	2B	2A	71	93	90	9	2	7.9	11.5	1
D. G.	+	—	Card.	2B	2A	85	90	84	?	2	9.3	11.0	1

* Predominantly cardiac.
† Predominantly chorea.
‡ Class 1, able to carry on ordinary activity; class 2A, activity slightly limited; class 2B, activity greatly limited; class 3, signs and symptoms of decompensation.
¶ Infection inactive before treatment started.
§ Not classified because of intercurrent infection.
‖ Persistently active infection.

TABLE 2.—*Data on Control Patients*

Patient	Activity			Class		Weight				Cystine, per Cent		
	Admission	Discharge	Localization	Admission	Discharge	Admission	Discharge	Ideal	Duration, Weeks	Initial	Final	Previous Attacks
R. G.	+	+	Card.	2B	2B	67	90	81	Per.	11.4	13.3	1
J. W.	+	+	Card.	2B	3	102	124	114	Per.	....	....	3
G. D.	—	+	Card.	2A	3	103	109	65	Per.	....	....	3
G. B.	+	—	Card.	2B	2A	61	84	80	28	....	....	1
L. F.	+	—	Card. chor.	2A	1	59	75	61	18	....	....	1
D. Gr.	+	—	Card.	2B	2A	66	82	80	18	....	....	1
F. B.	—	—	Chor.	2A	1	115	128	97	21	....	....	1
M. H.	+	+	Card.	2B	3	148	119	84	Per.	9.5	9.8	0
L. R.	+	—	Card.	3	2A	73	93	72	18	10.1	13.5	2
R. N.	+	—	Card.	2B	2A	39	46	46	6	....	....	1
T. C.	+	—	Card.	2A	2A	55	61	64	7	10.0	10.3	1
A. V.	+	+	Card.	2B	3	71	78	81	Per.	9.7	9.4	0
W. J.	+	+	Card.	2B	2B	95	125	94	Per.	11.2	10.2	2
R. P.	+	—	Card.	2B	2A	70	98	70	10	10.2	12.0	0
R. S.	+	—	Card.	2B	2B	72	74	78	10	10.9	10.8	2

2. The urine was examined for total sulfate and total sulfur and nitrogen content twice a week. This was necessary in order to establish that the sulfur was properly administered, absorbed, oxidized and excreted. Chemical and microscopic examinations of the urine for pathologic constituents were made at intervals of

two weeks. 3. The finger nails and the hair were examined for cystine content by Sullivan's [7] method at intervals of four to six weeks.

The patients were kept in the sanatorium for two to six weeks before receiving sulfur. Both treated and control patients were followed throughout the period of hospitalization.

RESULTS

Thirty patients have been observed since these studies were undertaken. Of the 15 treated patients, the activity of infection as indicated by

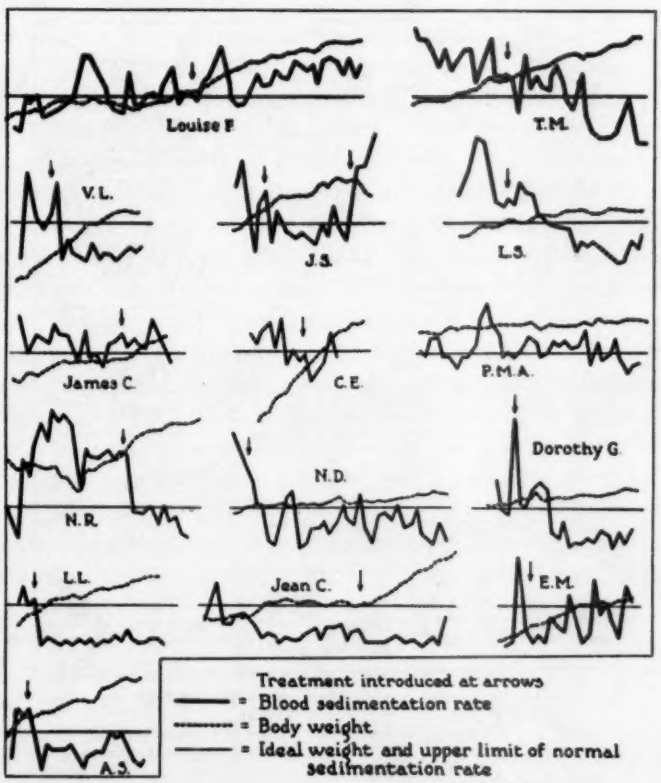

Chart 1.—Data for treated patients.

the sedimentation rate subsided in 13 and persisted in 2. In 9 of the 13 the infection became quiescent within six weeks after treatment was begun. Nine of the 15 control patients became free of active rheumatic infection during their hospitalization; the other 6 evidenced persistent infections and in 2 of these cardiac decompensation persisted. The clinical course of the entire series is summarized in tables 1 and 2 and charts 1 and 2.

7. Sullivan, M. X.: Pub. Health Rep., 1929, supp., p. 78.

The cystine content of the finger nails of many of the patients was below the average value but in the range existing in normal children. In both the sulfur-fed and the control group there was an increase in cystine content which coincided with clinical improvement, and in no instance was there a falling cystine value in an improving patient. The percentages of cystine are also listed in tables 1 and 2.

Routine blood counts and urinalyses yielded no relevant information. All the patients studied were free of anemia, leukocytosis and abnormal

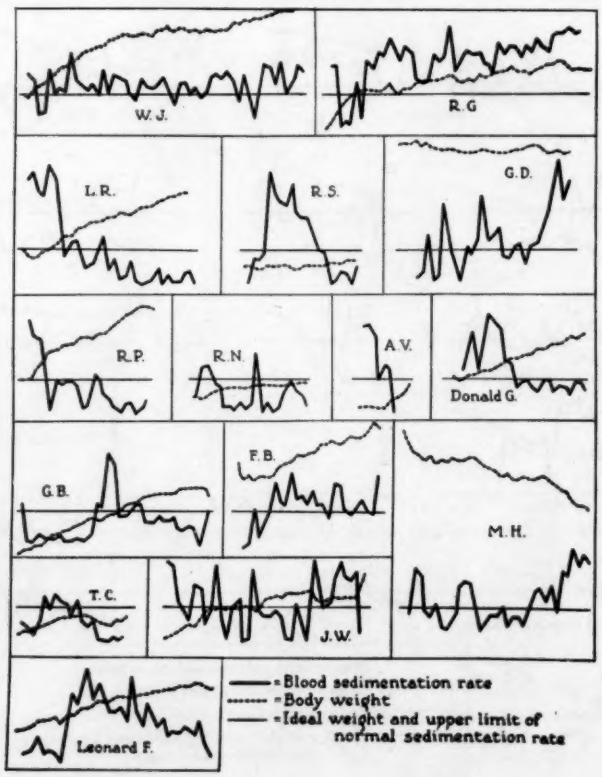

Chart 2.—Data for control patients.

substances in the urine. Determinations of urinary sulfur revealed an increased excretion of sulfate by the treated patients in the amount expected on the basis of the quantity of sulfur ingested.

COMMENT

In the series of patients studied there was apparently in general a more nearly complete recovery evidenced by the 15 sulfur-fed than by the 15 control children. An examination of chart 1 reveals that with

2 exceptions all were discharged with normal sedimentation rates. All patients left the sanatorium slightly overweight, which is considered to be a desirable margin of safety. In 4 of this group (N. R., L. L., A. S., and V. L.) the drop in sedimentation rate following treatment was strikingly prompt and was permanent for the duration of hospitalization. The control group (chart 2) included 9 children discharged with normal sedimentation rates and 6 with persistently active infections; 4 patients were underweight at discharge.

In view of the very wide individual variation, the series presented is not of sufficient size to eliminate the factor of chance in the selection of patients. However, it can be positively stated that colloidal sulfur does not prolong or complicate convalescence from acute rheumatic fever; on the other hand, it may in some instances accelerate recovery. Any part it plays in such a process is doubtless a nonspecific one, and there is no reason to believe that any sulfur deficiency exists in the patient with rheumatic fever. The results were not sufficiently positive to warrant a continuation of the study. The results of our studies on the partition of urinary sulfur are in accord with those of Senturia [2v,w] and of Freyberg, Block and Fromer [4] in that no deviations from the normal were found in a single analysis out of a great number performed. The results of analyses of the finger nails for cystine content indicate to us that this value is totally unrelated to administration of sulfur. About half of the patients had a low value for finger nail cystine which increased as the infection was controlled, and this took place to apparently the same extent in the control and the sulfur-fed group. The average initial cystine value for 24 patients was 10.4 per cent, the concentrations ranging from 7.9 to 13.4 per cent; and the average final value was 11.8 per cent, with a range from 9.4 to 13.5 per cent. Previous determinations performed by us on 53 healthy Chicago school children ranging in age from 6 to 15 years gave an average cystine content of 11.7 per cent, with extremes of 7.0 per cent and 15.4 per cent. Since there is such a wide normal variation and such a small difference in the normal and rheumatic organism; since the cystine content of nails is known to be lowered in a variety of debilitated states; since the cystine content may be low in the absence of any pathologic condition, and since the analytic procedure requires a certain degree of finesse and more time and apparatus than are available to the ordinary clinical laboratory, we feel that the usefulness of it is most limited.

The site and mode of action of colloidal sulfur are at present obscure. Nevertheless, some hypotheses may be advanced. The gastrointestinal tract has frequently been incriminated as a portal of entry of rheumatic infection, and a high blood sedimentation rate is accompanied by an increased fibrinogen content of the blood, which in turn is evidence of a disturbance in the liver. Since orally administered colloidal sulfur is

promptly absorbed from the intestine and oxidized in the liver, its possible effect as a metabolic whip must be considered. In this connection may be noted the consistently greater gain in weight of the sulfur-fed patients.

SUMMARY AND CONCLUSION

A colloidal sulfur–polysulfide preparation has been tested therapeutically on 15 children convalescent from acute rheumatic fever. The progress of these patients was checked against that of 16 control patients. The sulfur in no case affected recovery adversely, and in certain cases it appeared to enhance it. However, the results were not sufficiently striking to rule out the factor of chance in the selection of patients and to warrant the continuation of the study.

Children with rheumatic fever present no abnormalities in sulfur metabolism. Certain patients have a low cystine content of the finger nails which increases during clinical improvement whether or not sulfur is administered. The advisability of performing cystine analyses is questionable.

Whatever action colloidal sulfur has is undoubtedly nonspecific. If it has an effect, the effect is probably on the intestine or on the liver.

DIABETIC DWARFISM

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BOSTON

One of the distinctive features of juvenile diabetes is its occurrence in a period of life in which the person lives under the conditions of growth and development. Thus it is evident that there are three possibilities: (1) Growth and development may influence the course of diabetes, (2) diabetes may influence the growth and development of the child or (3) there may be no interrelationship.

That deviations from normal trends occur in diabetes was shown as early as 1925. Joslin, Root and White,[1] reporting on the growth and development of juvenile diabetic patients, observed that a group of long duration preinsulin survivors exhibited retardation of growth, yet the average height of the entire series exceeded the Baldwin and Wood standard average for their age. It was suggested at this time that the potential diabetic child was tall and that in certain cases of long duration stunting resulted. In the sixteen years which has elapsed since this early report, repeated analyses of the growth data of the juvenile patients of this clinic have borne out the earlier observations that overheight at onset is characteristic of diabetes in childhood but that significant stunting eventually develops in 1 out of every 10 patients.

Great diversity of opinion exists concerning the underlying mechanism of retardation. One of us (P. W.[2]), reporting a series of 94 cases in 1939, concluded that fatigue of the pituitary is the most logical explanation. Another of us (R. W.[3]) classified the dwarfism in 4 of his 107 diabetic patients as a congenital anomaly. Boyd and Kantrow,[4] who

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1. Joslin, E. P.; Root, H. F., and White, P.: Growth, Development and Prognosis of Diabetic Children, J. A. M. A. **85**:420-422 (Aug. 8) 1925.

2. White, P.: Endocrine Manifestations in Juvenile Diabetes, Arch. Int. Med. **63**:39-53 (Jan.) 1939.

3. Priesel, R., and Wagner, R.: Fehlbildungen beim Diabetes Mellitus der Jugendlichen, Ztschr. f. Kinderh. **49**:419-428, 1930.

4. Boyd, J. D., and Kantrow, A. H.: Retardation of Growth in Diabetic Children, Am. J. Dis. Child. **55**:460-471 (March) 1938.

reported 19 cases, concluded that control of diabetes prevents retardation and that it is not a consequence of endocrine disturbance. Gibson and Fowler,[5] reporting on 8 patients (4 boys and 4 girls) from 16 to 20 years of age, described a syndrome of infantilism apparently due to hypofunction of the anterior lobe of the pituitary. Warkany and Mitchell[6] suggested that parallel deficiencies rather than a primary and a subordinate condition occur. Sundal[7] interpreted the condition of a 6 year old diabetic child with retardation of growth and hepatomegaly as a combination of glycogen storage disease and diabetes.

It is the purpose of this study to analyze the patients whose heights have been retarded, to differentiate them according to the causation of the dwarfism and to outline its treatment and the effect on the course of the disease. Because diabetic dwarfism has been explained on the basis of an endocrine imbalance, as due to inadequate nutrition and as an anomaly independent of the diabetic anlage, a series of nondiabetic and diabetic patients reporting in sequence were compared before the dwarfish group was analyzed. In order to establish some basic appraisal of the constitutional peculiarities of the diabetic child, the following characteristics were observed: height, weight, sexual development, condition of the teeth and gums, size and sounds of the heart, size of the liver, appearance of the skin and presence of visible stigmas. A total of 359 children were examined, 200 diabetic (100 boys and 100 girls) and 159 nondiabetic (81 boys and 78 girls). The 200 diabetic patients included dwarfish children, in order that a cross section of our entire group might be presented. The ages of the diabetic boys varied from 4 to 20 years, of the diabetic girls from 6 to 21, of the nondiabetic boys from 4 to 16 and of the nondiabetic girls from 3 to 14. (The absolute figures within a year of life were not identical.) The controls were derived from underprivileged and privileged groups, including children from the Prendergast Preventorium, the Ellis Memorial Club and a private school.

I. COMPARISON OF NORMAL CHILDREN AND DIABETIC CHILDREN

RELATIONS OF VARIOUS FEATURES

A. Age-Height Relationship.—The relationship between age and height was considered first. Three different standards were used, namely, those of Baldwin and Wood, Engelbach and Meredith. The

5. Gibson, R. B., and Fowler, W. M.: Infantilism and Diabetes Mellitus: Report of Eight Cases, Arch. Int. Med. **57**:695-707 (April) 1936.

6. Warkany, J., and Mitchell, A. G.: Relation of Endocrine Disturbances to Certain Heredodegenerative Symptoms, Am. J. Dis. Child. **55**:231-243 (Feb.) 1938.

7. Sundal, A.: Fall von Wachstumshemmung bei einem Diabetiker, Kinderärztl. Praxis **10**:93 (Feb.) 1939.

heights for age of the 80 nondiabetic boys were plotted in chart 1 *A*; of the 90 diabetic boys, in chart 1 *B*. The charts of the 76 nondiabetic girls and of the 100 diabetic girls are not included in this paper. It is obvious that the heights of the nondiabetic boys followed the prediction closely with a certain tendency to plus variations, while in the diabetic group, in contrast, there were a prevalence of minus variations and some

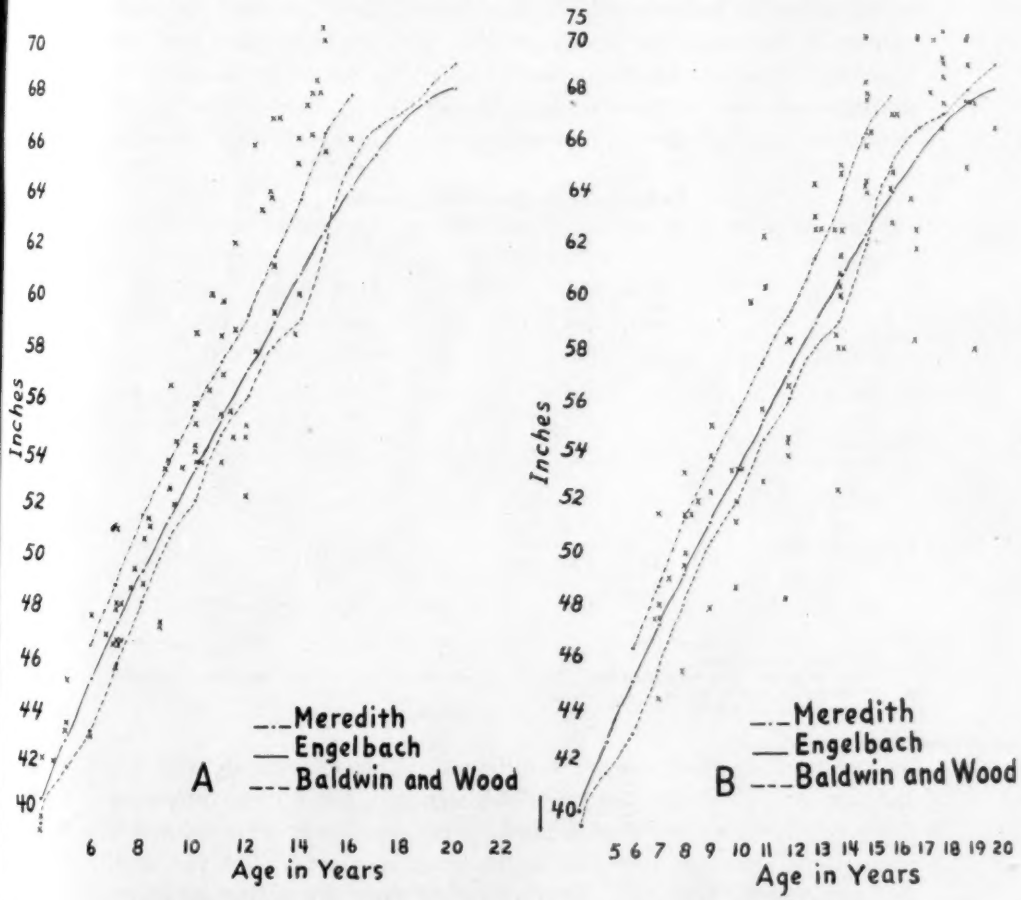

Chart 1.—Relation between age and height (*A*) for 80 nondiabetic boys and (*B*) for 90 diabetic boys.

actual dwarfism. The charts of the girls, which are not included in this paper, also showed a predominance of minus variations. As there were plus variations as well among the diabetic children, the width of variation was definitely greater in the diabetic than in the nondiabetic group.

The exact figures for age-height relationship for the two groups of children according to our three standards are given in table 1. The

number of plus variations markedly decreases in the diabetic group with the use, in order, of the Baldwin and Wood, the Engelbach and the Meredith standard. The number of minus variations is nearly the same for diabetic boys according to the standard of Baldwin and Wood and of Engelbach but distinctly higher according to the standard of Meredith. A great decrease in minus variations occurs among the girls when one applies either the Baldwin and Wood or the Engelbach standard. A comparison of the minus deviations obtained with the Engelbach and the Meredith standard cannot be made, since the Meredith standard is available only for the ages between 6 and 16 and many of the minus deviations occurred after the sixteenth year. The nondiabetic group of

TABLE 1.—*Age-Height Relationship*

	Diabetic Children				Nondiabetic Children			
	No. of Subjects	Range of Age	Variations		No. of Subjects	Range of Age	Variations	
			Plus	Minus			Plus	Minus
Meredith								
Boys	68	7-16	2.9 2*	20.6 14	75	6-16	5.3 4	8.0 6
Girls	78	6-16	1.3 1	20.5 16	73	6-15	8.2 6	23.2 17
Engelbach								
Boys	90	7-20	16.6 15	5.6 5	80	4-16	25.0 20	1.3 1
Girls	100	6-20	3.0 3	15.0 15†	76	5-18	14.5 11	2.6 2
Baldwin and Wood								
Boys	90	7-20	21.0 19	6.7 6	80	4-16	27.4 22	0
Girls	100	6-20	7.0 7	8.0 8‡	76	5-18	27.6 21	0

* Number of subjects.
† Very retarded girls were included. Therefore, the deviations are not less than according to the Meredith standard.
‡ More than —4 inches.

boys showed no great numerical difference in plus variations with the Baldwin and Wood and the Engelbach standard, but a great difference if the Meredith figures were applied. The nondiabetic girls showed a proportional decrease according to the three standards (27.6 per cent, 14.5 per cent, 8.2 per cent). In the columns where the minus variations are recorded, the values of 17 and 23 per cent (nondiabetic girls, standard of Meredith) do not conform.

B. Height-Weight Relationship.—The relationship between height and weight in boys is shown in chart 2. The standards were derived from different sources, including Camerer-von Pirquet and Kornfeld.[8]

8. Kornfeld, W.: Durchschnittswerte der wichtigsten Körpermasse und wichtiger physiologischer Daten bei Kindern aller Altersstufen, Vienna, Wilhelm Maudrich, 1932.

The diabetic children were slightly heavier for height than the nondiabetic. Higher grades of obesity were limited to girls. One naturally asks if this is the result of overnutrition, an accentuation of a normal, physiologic gain in weight in a certain period (so-called period of "third filling") or a manifestation of a specific endocrine disorder. Conclusions cannot be drawn from the data available in this study.

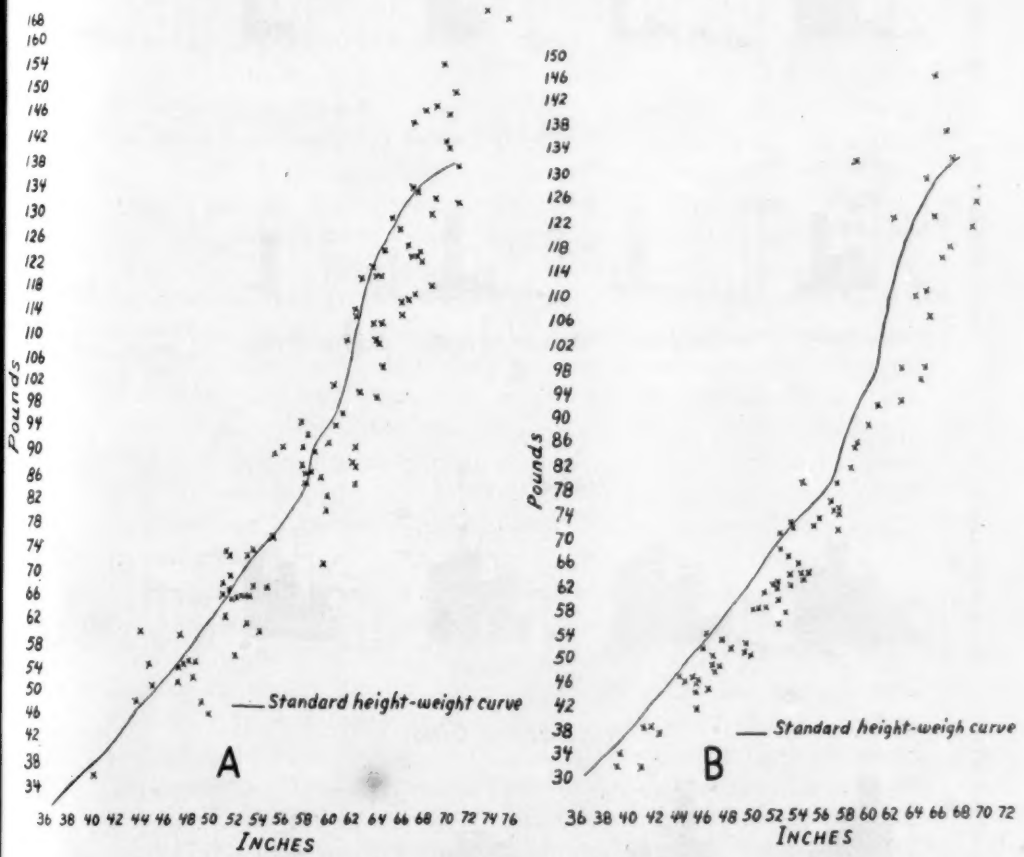

Chart 2.—Relation between height and weight (*A*) for 100 diabetic boys and (*B*) for 80 nondiabetic boys.

C. Sexual Development.—A comparison of the order and extent of sexual development of our two groups of children is important. We are not unmindful of the fact that great variations exist even among nondiabetic persons. Such deviations include the time of onset, degree and order of appearance of the single components of development. The comparison of the diabetic and the nondiabetic group is made in chart 3. The children included in this study were from 7 to 16 years of age. Sixty-six

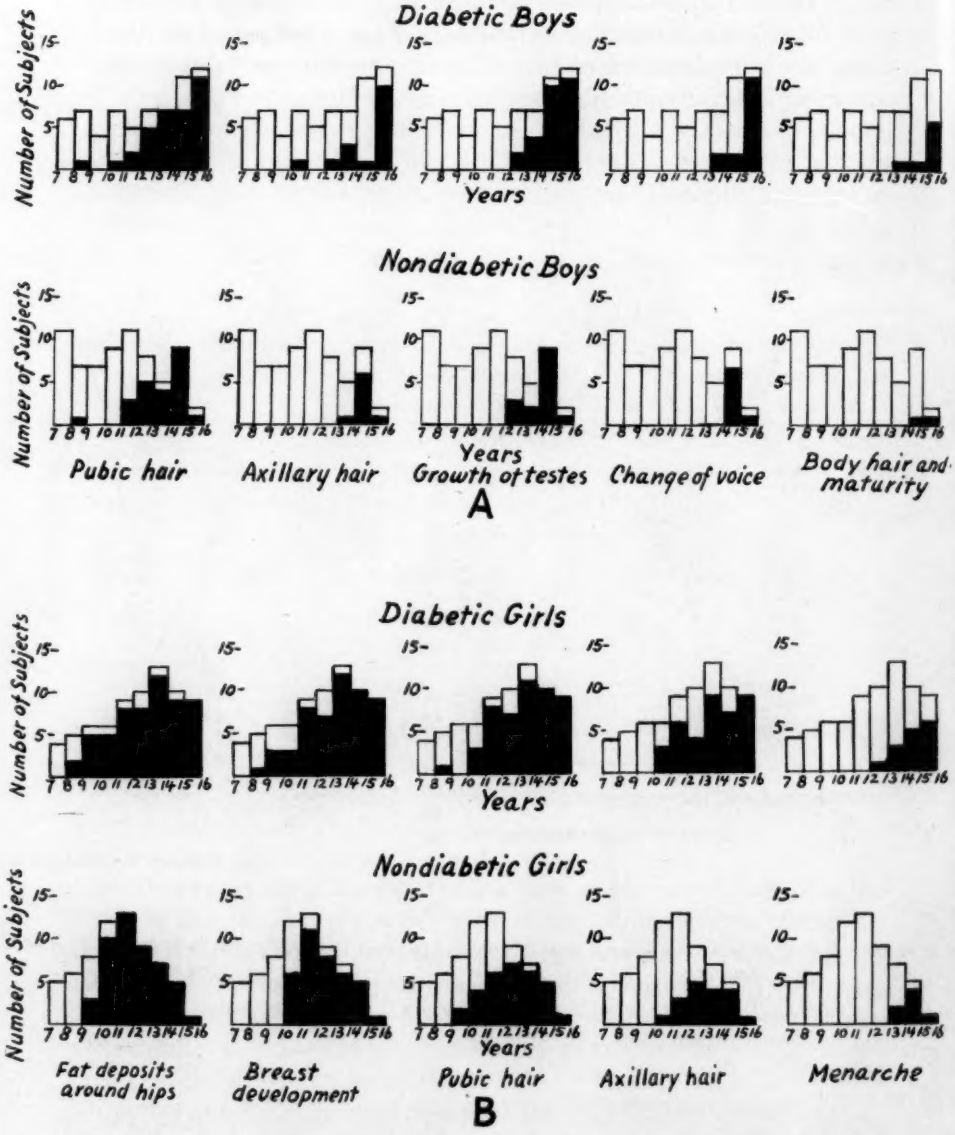

Chart 3.—Sexual development (*A*) of 66 diabetic and of 69 nondiabetic boys and (*B*) of 72 diabetic and of 66 nondiabetic girls.

diabetic boys were compared with 69 nondiabetic boys, and 72 diabetic girls with 66 nondiabetic girls. All diabetic girls in this group over 16 years of age were completely developed. A greater lag in development was observed among the boys than among the girls. The incidence of subnormal development in the boys was influenced by the number of dwarfish boys included in this series.

The graphic analysis of the sexual development consisted of plotting the presence of each component in the order of its normal appearance: for boys, pubic hair, increments in testicular size, axillary hair, change of voice, maturity and body hair; for girls, rounding of hips, breast development, pubic and axillary hair and menarche. The presence of the respective component but not the degree was recorded. An earlier appearance of the secondary sex characteristics was observed in the diabetic patients. If, however, one considers the whole course of sexual development from the beginning to complete maturity, the diabetic group exhibited a delay. This is probably greater because of the inclusion of retarded children who were receiving special care at this time. Thus, in spite of the earlier onset in some of the cases, sexual development was delayed 23 times among the diabetic boys and 13 times among the diabetic girls, whereas it was delayed only twice among the nondiabetic boys and not once among the girls. Precipitated development occurred in 7 diabetic boys and 4 diabetic girls, in none of the normal boys and in only 1 of the normal girls. Dysharmony of the regular sequence occurred in 6 diabetic boys and 7 diabetic girls and in 3 normal boys and 3 normal girls.

Some years ago one of us (P. W.[9]) showed that the diabetic child is frequently overheight at onset of the disease. An early sexual development is consistent with this overgrowth. One naturally asks what is the mechanism underlying the earlier development in the person with diabetes. 1. Is it earlier awakening of the pituitary gland? Hyperactivity of the pituitary might precipitate diabetes, overgrowth and early development. That retardation of growth and development ensue is no contradiction, since fatigue of an overactive organ is known to exist. 2. Or is this a variation in the end organ response? 3. Or are the early sexual development and variations from the normal order and diabetes superimposed chromosomal predispositions? The last conception may be supported by the presence of certain somatic stigmas. Whatever the explanation, the sexual development appears to be slightly precipitated in the diabetic child at onset of the disease, but it may become delayed with duration of diabetes.

9. White, P.: The Potential Diabetic Child, J. A. M. A. **88**:170-171 (Jan. 15) 1927.

D. Teeth and Gums.—The next problem with which we are concerned is the comparison of the condition of the teeth and gums of the diabetic and of the nondiabetic group. Several observers (Rudy and Cohen [10] and Stein [11]) have shown that diabetic children have comparatively little caries. The influence of the diet alone is probably not of first importance, since the diet of diabetic children differs little from that of normal children. On the other hand, it is well known that the occurrence of caries is familial. The onset, extent and distribution of caries in the child often coincide strikingly with those of one or the other parent.

The distribution of caries and of pyorrhea in our two groups is shown in tables 2, 3 and 4. Table 2 deals with both boys and girls, and tables

TABLE 2.—*Teeth and Gums of Diabetic and of Nondiabetic Children*

	Six Year Molar Only	Other Teeth * +	Other Teeth * ++	Pyorrhea
Diabetic Children				
	Caries (168 Subjects)			(200 Subjects)
Percentage	8.4	31.6	7.1	26.5
Number	14	53	12	53
Total percentage		38.7		
Nondiabetic Children				
	Caries (96 Subjects)			(159 Subjects)
Percentage	10.4	42.7	6.3	1.3
Number	10	41	6	2
Total percentage		49.0		

* Six year molar included.

3 and 4 show the respective figures for each sex. We have studied caries in the permanent teeth only, since the onset of diabetes usually occurs after the eruption of the deciduous teeth. Caries is subdivided into caries restricted to the six year molars, mild caries involving more than this tooth (+) and more severe generalized caries (++).

There was a predominance of caries amounting to 10 per cent among the nondiabetic children. Its incidence in the six year molar, the oldest tooth in the permanent dentition, was about the same in both groups. One may describe this form as almost "physiologic." The predominance of caries in the nondiabetic children was due to the higher incidence in girls. This linkage justifies the inclusion of this problem in our con-

10. Rudy, A., and Cohen, M. M.: The Oral Aspects of Diabetes Mellitus, New England J. Med. **219**:503-508 (Oct. 6) 1938.

11. Stein, G., in discussion on Priesel.[30]

stitutional analysis. Perhaps the earlier onset of puberty in girls was responsible for the earlier decay of the teeth. Why there was less caries in the diabetic child is not clear. A possible explanation is hypo-

TABLE 3.—*Teeth and Gums of Diabetic Children*

	Six Year Molar Only	Other Teeth * +	Other Teeth * ++	Pyorrhea (100 Subjects)
Boys				
Caries (82 Subjects)				
Percentage	11.0	28.0	9.8	24.0
Number	9	23	8	24
Total percentage		37.8		
Girls				
Caries (86 Subjects)				
Percentage	5.8	35.0	4.7	29.0
Number	5	30	4	29
Total percentage		39.7		

* Six year molar included.

TABLE 4.—*Teeth and Gums of Nondiabetic Children*

	Six Year Molar Only	Other Teeth * +	Other Teeth * ++	Pyorrhea (81 Subjects)
Boys				
Caries (46 Subjects)				
Percentage	8.8	30.0	2.2	1.2
Number	4	14	1	1
Total percentage		32.2		
Girls				
Caries (50 Subjects)				
Percentage	12.0	54.0	10.0	1.3
Number	6	27	5	1
Total percentage		64.0		

* Six year molar included.

gonadism, suggested by the delayed progress in development in diabetic girls in whom the duration of the disease is long.

Pyorrhea is frequent in diabetic persons, in contrast to the low incidence of caries. Pyorrhea is not a uniform etiologic and morphologic entity. One type—the "Schmutz pyorrhea"—appears to be particularly frequent with neglected diabetes. It is possible that the peridontal tissues

of a person with continuously decompensated diabetes become more vulnerable and liable to infection, and it is also true on the whole that the better the control of the diabetes, the better the control of pyorrhea. Another type of pyorrhea seen in diabetic patients is characterized by diffuse alveolar atrophy. Lack of diabetic control alone cannot be the only explanation for the frequent occurrence of pyorrhea. Two facts are opposed to this simple interrelationship: first, the presence of the latter type of pyorrhea in members of diabetic families who do not have the disease and, second, the differences in the frequency of this pyorrhea in different parts of the world. It was pointed out by one of us (R. W.[12]) that severe forms of pyorrhea in diabetic children, in contrast to nondiabetic children, are much more frequent in Vienna than in this

TABLE 5.—*Incidence of Systolic Murmurs*

	Diabetic Children (200)					
	Pulmonic		Apex		Congenital	
	Boys (100)	Girls (100)	Boys (100)	Girls (100)	Boys (100)	Girls (100)
Percentage	15.0	36.0	0	2.0	1.0	1.0
Number	15	36	0	2	1	1
Total percentage	25.5		1.0		1.0	

	Nondiabetic Children (159)					
	Pulmonic		Apex		Congenital	
	Boys (81)	Girls (78)	Boys (81)	Girls (78)	Boys (81)	Girls (78)
Percentage	3.8	7.7	2.6	6.4	0	0
Number	3	6	2	5	0	0
Total percentage	5.7		5.0		0	

country. Three explanations may be considered: (1) specific infection; (2) racial differences; (3) different dietetic habits. We have no data concerning the first two explanations. It is possible that the high intake of vitamins and minerals is responsible for the lower incidence of severe pyorrhea in this country. Rudy and Cohen,[10] too, came to the latter conclusion. Pyorrhea of unidentified type was twenty-five times as frequent in the diabetic group as in the nondiabetic.

E. Heart.—A distinction has been made (table 5) between (*a*) simple accidental or functional systolic murmurs in the pulmonic area, which are so often heard during the developmental period and which are often associated with sinus arrhythmia; (*b*) systolic murmurs with the maximum intensity at the apex of the heart accompanied by an accentuation of the second pulmonic sound, which are probably due to

12. Wagner, R.: Peculiarities in Therapy of Diabetic Children on Two Continents, read before the Suffolk District Medical Society, Jan. 25, 1939.

organic lesions, and, finally, (*c*) murmurs heard all over the precordium, possibly due to congenital cardiac lesions. Murmurs resulting from organic disease were infrequent, owing to the apparently rare occurrence of rheumatic heart disease among persons with diabetes, but accidental murmurs were heard more frequently.

F. Liver.—Hepatomegaly in juvenile diabetes has been observed by several investigators. White [13] in 1932 suggested that the enlargement was due to fat. Hanssen,[14] the first to demonstrate its control with protamine zinc insulin, also thought it was due to fat infiltration. Marble, White, Bogan and Smith [15] in 1938, reviewing the data of this clinic again, left the question open. Boucomont, Serre and Godlewski [16] called it a manifestation of endocrine imbalance.

Stetson and Ohler [17] found glycogen intracellularly in a biopsy of a liver. Young [18] and Marks and Young [19] have shown that the livers and muscles of rabbits treated with large doses of anterior pituitary extract had a very high glycogen content. Mauriac [20] has described cases of dwarfism with hepatomegaly in diabetic children in which he explained the hepatomegaly as a consequence of disturbance in the carbohydrate metabolism and the dwarfism on the basis of a failure of fixation and storage of vitamin A in the liver.

Whereas the experiments of Young and of Marks and Young suggest the possibility that the mechanism of production of hepatomegaly in diabetes is an abnormal glycogen storage due to a hyperactive pituitary gland, an increased fat deposit in the liver in various animals following the administration of anterior pituitary extract was observed by Best

13. White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932, p. 66.

14. Hanssen, P.: Enlargement of the Liver in Diabetes Mellitus, J. A. M. A. **106**:914-916 (March 14) 1936.

15. Marble, A.; White, P.; Bogan, I. K., and Smith, R. M.: Enlargement of Liver in Diabetic Children: Its Incidence, Etiology and Nature, Arch. Int. Med. **62**:740-750 (Nov.) 1938.

16. Boucomont, J.; Serre, H., and Godlewski, M.: Retard corporel et psychique avec hépatomégalie considérable et hypertrophie des glandes salivaires chez un jeune diabétique, Arch. Soc. d. sc. méd. et biol. de Montpellier **19**:236-242 (May) 1938.

17. Stetson, R. P., and Ohler, W. R.: Hepatomegaly and Jaundice in Juvenile Diabetes, New England J. Med. **217**:627-629 (Oct. 14) 1937.

18. Young, F. G.: The Influence of Glycotropic Pituitary Extracts on Liver Glycogen, J. Physiol. **90**:20P (June 17) 1937.

19. Marks, H. P., and Young, F. G.: The Influence of Anterior Pituitary Extracts, Injected Either With or Without Insulin, on the Glycogen Contained in the Livers of Fasting Young Rabbits, J. Physiol. **93**:61-73 (June 14) 1938.

20. Mauriac, P.: Hépatomégalies de l'enfance avec troubles de la croissance et du métabolisme de glucides, Paris méd. **2**:525-528 (Dec. 29) 1934.

and Campbell.[21] A close relationship between glycogen storage disease and diabetes has been shown by one of us (R. W.).[22] He described a patient with typical glycogen storage disease in whom diabetes developed later. In a recently published review he compared glycogen storage disease with the diabetes of the Houssay dog.

A simple explanation and one which appears logical is based on a theory formulated in 1932 by one of us (P. W.[13]). This theory, which concerns an imbalance of fat metabolism, has been strengthened by biopsy of an enlarged liver of a young person with diabetes. The specimen of liver was obtained during the course of an exploratory laparotomy for an abdominal mass. It should be emphasized that this operation was done three days after the patient's entrance into the hospital. Histologic examination showed an excess of fat and glycogen. On chemical analysis this amounted to 10 per cent fat and 12 per cent glycogen. Confusion in interpretation of biopsy data arises because specimens are obtained during a period of controlled diabetes, since these patients are prepared for a surgical procedure. It seems logical to assume that the most advanced stage of uncontrolled diabetes is characterized by an excess of depot fat in the liver. As the control of diabetes improves, the amount of fat decreases, whereas the amount of glycogen increases and the final stage (controlled diabetes) is characterized by glycogen almost entirely replacing fat. This explanation of hepatomegaly as caused by an excessive fat deposit holds true for one group of diabetic persons, the decompensated, but other explanations must be considered for persons with compensated diabetes.

An enlarged liver was a not infrequent finding in the stunted diabetic children. The incidence in diabetic and in nondiabetic children is shown in tables 6 and 7.

G. Skin.—The lesions of the skin to be expected in the diabetic child which are more or less specific for diabetes itself, namely, xanthosis, xanthomas and necrobiosis lipoidica diabeticorum, were the exception in this group. Their expected absence in the nondiabetic children was confirmed. Anomalies of the skin, epithelial stigmas, will be discussed in the following section.

H. Stigmas.—Classification of stigmas is made according to their germinal origin: mesenchymatous, epithelial and mixed stigmas and defects. The mesenchymatous lesions and their incidence (in percentage) in the 100 diabetic boys, 100 diabetic girls, 81 nondiabetic boys and 78 nondiabetic girls are as follows: marked brachycephalus (0, 2.0, 0, 0); Dupuytren's contracture, isolated contracture of the fifth finger

21. Best, C. H., and Campbell, J.: The Effect of Anterior Pituitary Extracts on the Liver Fat of Various Animals, J. Physiol. **92**:91-110 (Feb. 16) 1938.

22. Wagner, R.: Die Speicherkrankheiten (Thesaurismosen), Ergebn. d. inn. Med. u. Kinderh. **53**:586-684, 1937.

(1.0, 2.0, 0, 0); curved fifth finger (9.0, 5.0, 6.2, 2.6); brachydactylia (2.0, 2.0, 1.2, 0); arachnodactylia (0, 1.0, 0, 0); hereditary clubbing of the thumb (0, 1.0, 1.2, 0); scaphoid scapula (14.0, 5.0, 17.2, 7.7); fusions and other anomalies of the ribs and of the thorax, such as pigeon breast (0, 0, 2.5, 1.3) and cobbler breast (0, 0, 5.0, 1.3); knock knees (0); malocclusion (11.0, 12.0, 14.8, 11.6); arched palate (1.0, 4.0, 2.5, 0); ear nodules (10.0, 1.0, 5.0, 2.6); Darwin's tubercle (0, 0, 2.5, 0);

TABLE 6.—*Incidence of Hepatomegaly in Diabetic and in Nondiabetic Boys and Girls*

	Diabetic Children (200)							
	Boys (100)				Girls (100)			
	1 Cm.	2 Cm.	3 Cm.	>3 Cm.	1 Cm.	2 Cm.	3 Cm.	>3 Cm.
Percentage	14.0	22.0	11.0	4.0	12.0	22.0	14.0	3.0
Number	14	22	11	4	12	22	14	3
Total percentage			15.0				17.0	
	Nondiabetic Children (159)							
	Boys (81)				Girls (78)			
	1 Cm.	2 Cm.	3 Cm.	>3 Cm.	1 Cm.	2 Cm.	3 Cm.	>3 Cm.
Percentage	2.1	6.4	7.4	1.2	2.6	10.0	2.6	0
Number	2	5	6	1*	2	8	2	0
Total percentage			8.6				2.6	

* Completely infantile.

TABLE 7.—*Incidence of Hepatomegaly in Diabetic and Nondiabetic Children*

	Diabetic Children (200)			Nondiabetic Children (159)		
	Percentage	Number	Total Percentage	Percentage	Number	Total Percentage
1 cm.	13.0	26	13.0	2.5	4	2.5
2 cm.	22.0	44	22.0	8.2	13	8.2
3 cm.	12.5	25	16.0	5.0	8	5.6
>3 cm.	3.5	7		0.6	1	

pitcher ears (10.0, 0, 11.1, 0); hyperextensibility of joints (0); congenital dislocation of the patella (0); hernia (0); cryptorchidism (2.0, 0, 0). The epithelial group includes adherent and missing ear lobes (6.0, 4.0, 5.0, 0), webbed toes (0, 1.0, 1.2, 1.3), hypoplasia of dental enamel (0), missing tooth buds (0), ichthyosis (0), epicanthus (3.0, 1.0, 1.2, 1.3), congenital cataracts (0), hypermetropia (0, 0, 0, 1.3), astigmatism with strabismus (3.0, 1.0, 4.9, 3.9), accessory nipples (2.0, 1.0, 0, 0), pendulous breasts (1.0, 0), hypertrophy of the breasts (0) and multiple nevi (4.0, 1.0, 0, 0). In some instances multiple stigmas and defects, mesenchymatous and epithelial in origin, occurred (1.0, 2.0, 0, 0). Gross defects, such as diaphragmatic hernia, congenital

cardiac heart lesions, congenital megacolon and epilepsy (1.0, 1.0, 0, 1.0) and systemic disease, such as Friedreich's ataxia, have been infrequently observed.

Numerically we found very little predominance of the stigmas in the diabetic group. Certain stigmas, however, are more or less specific. Dupuytren's contracture was found only in the diabetic children. Other mesenchymatous stigmas which appeared more frequently in the diabetic child are curved fifth finger, brachydactylia and marked brachycephalus. A stigma seen more frequently in the diabetic group, especially in the boys, is the ear nodule on the lateral aspect of the auricle. Isolated scaphoid scapula, malocclusion of the jaws, Darwin's tubercle and pitcher ears were not characteristic of the diabetic child. The last-mentioned stigma was seen only in boys. All the other mesenchymatous stigmas listed seem to be unimportant. Since roentgen examinations of the skeleton were not made for all the nondiabetic children, we must be careful about drawing conclusions.

The epithelial group seems to be of less significance than the mesenchymatous. In 1 diabetic boy we observed a small appendage on the lateral aspect of the neck, probably due to an anomaly in the closure of the branchiogenic cleft, and in 1 diabetic girl a congenital cataract with nystagmus.[23]

Mixed stigmas and defects were observed in 3 diabetic children, a boy and 2 girls. The boy showed marked brachydactylia and had been previously treated for myxedema. One of the dwarfish girls had brachycephalus, brachydactylia and a rare lesion of the bones with a fracture. No definite roentgenologic diagnosis was made. Scurvy and aseptic necrosis (similar to Köhler's disease and to Schlatter-Osgood disease) were considered. The second girl had hereditary kyphoscoliosis and a peculiar malformation of the hands. This was diagnosed as a questionable chondrodystrophy but possibly represents another congenital genopathy. Such conditions are certainly not characteristic of or specific for diabetes and are seen as well in nondiabetic children.

The only definite fact we can establish from our investigation is that certain mesenchymatous stigmas seem to occur slightly more frequently in diabetic children than in the nondiabetic ones.

SUMMARY

The constitution of the diabetic child is somewhat different from that of the nondiabetic child. From a comparison of 200 diabetic children with 159 nondiabetic children, the following conclusions can be drawn:

23. In juvenile diabetic patients, not included in this particular report, we observed a fusion of two ribs, a shovel rib, a congenital dislocation of the patella and a congenital diaphragmatic hernia; many had hyperextensibility of the joints.

1. In spite of the fact that overheight is characteristic of juvenile diabetes at the onset, a certain number of diabetic children become stunted. The incidence amounts to 5 to 10 per cent. There is the same tendency toward plus variations in the diabetic as in the nondiabetic group. 2. The weight-height relationship is normal in diabetic children except for one group of girls. This group has a specific form of obesity. 3. The onset of sexual development of the average diabetic child—the diabetic child of normal height and weight—tends to occur precociously, but sexual development may not progress at the normal rate. There is also retardation of the sexual development in nearly all retarded diabetic children, exactly as in many retarded nondiabetic children. Dysharmonic development (disturbance in the order of appearance of the secondary sex characteristics) is seen nearly twice as often in the diabetic children as in the nondiabetic. 4. Dental caries is less frequent in diabetic than in nondiabetic children. The nondiabetic predominance of caries applies only to girls. Pyorrhea occurs much more frequently in children with diabetes. 5. Accidental (functional) systolic murmurs in the pulmonic area are found much more frequently in diabetic children. Rheumatic heart disease is very rare in such children. 6. Enlargement of the liver is common in diabetic children and adolescents. 7. Certain mesenchymatous stigmas are slightly more prevalent in diabetic children, but gross defects and anomalies are seldom seen.

II. ANALYSIS OF DIABETIC DWARFISM

Although the total incidence of retardation in diabetic children is not great, since more than 90 per cent grow and develop normally, the medical, social and economic importance of the problem warrants its special consideration.

The total number of retarded children examined amounted to 118, or 8.3 per cent, of our first 1,407 patients. Seventy-five, or 63.5 per cent, were boys and 43, or 36.5 per cent, girls.[24] Since the distribution of diabetes in childhood is equal in the two sexes, the prevalence of the male sex among the retarded diabetic children is a true one. The tendency of the male toward dwarfism may have the same underlying cause as his greater tendency toward congenital anomalies, or it may be explained by the fact that the period of pubescence lasts longer than in girls.

First of all, analyses of the height-age and height-weight relationships are given; then a study is made of the peculiarities of the diabetes in this group, its complications, the diabetic status and the laboratory findings.

24. Complete data were not available for all the children; so the boys do not number 75 and the girls 43 in every table.

A clinical classification of our retarded group, the treatment of the retardation and the response of the diabetes to the therapy are discussed.

All children who showed a retardation in height of 4 inches (10 cm.) or more according to the Engelbach standard have been classified by us as retarded. The Engelbach standard has been chosen because it represents the median values between the Baldwin and Wood and the Meredith figures. We are aware that a retardation of 4 inches represents only an arbitrary value. However, this amount of deviation in most cases lies below the lowest limits of the Baldwin and Wood and of the Engelbach standard. In the case of the former standard there are only a few children between 12.5 and 15.5 years of age whose heights lie above the lowest limits.

True dwarfism in childhood constitutes a failure to attain by 30 per cent standard average height. None of the patients in our group were retarded more than 30 per cent. Seventy-five patients were retarded between 10 and 19 per cent and 5 between 20 and 30 per cent.

HEIGHT-AGE AND HEIGHT-WEIGHT RELATIONSHIPS

Concentration of retardation in one age group is characteristic of girls; scattering is characteristic of the boys. Thus we observe in chart 4 *B* that the signs representing the girls are concentrated in the age period between 12.5 and 15 years, while those for the boys (chart 4 *A*) are scattered over the whole childhood period, showing a certain condensation between 15 and 17.5 years. Another difference is the presence of a group of boys only slightly retarded (0 to 9 per cent). No corresponding group is present in the girls' chart. The boys with retardation between 0 and 9 per cent represent a group classified later as having "transitory (genuine) infantilism." More boys than girls are so classified.

Leanness rather than obesity was characteristic of these children at the beginning of their retardation; 23.9 per cent of the boys and 31.0 per cent of the girls were more than 10 per cent underweight; only 8.7 per cent of the boys and 26.2 per cent of the girls were more than 10 per cent overweight (table 8).

The ratio between underweight and overweight becomes reversed with progressive retardation (table 9). The girls particularly show a high percentage of overweight at the time of maximal retardation. High degrees of obesity were extremely rare among the boys, but among the girls there were 12 out of 43 (or 27.9 per cent) with obesity of more than 20 per cent. It is the sort of obesity mentioned in a previous section (page 670). The distribution of patients with obesity was different for the two sexes, as was the distribution of the patients who were underheight. The girls showing obesity were definitely concentrated in one group, while the boys were scattered over the entire childhood period.

In contrast to the higher incidence of obesity in the girls (17.3 per cent boys and 44.2 per cent girls), there was a definite prevalence of leanness among the boys (13.1 per cent boys and 2.3 per cent girls). No girl was more than 20 per cent underweight. The leanness among the boys does not mean that they were markedly undernourished or showed poorer control of their diabetes. The greater weight of the girls was simply the physiologic state before maturity (the period of the third filling).

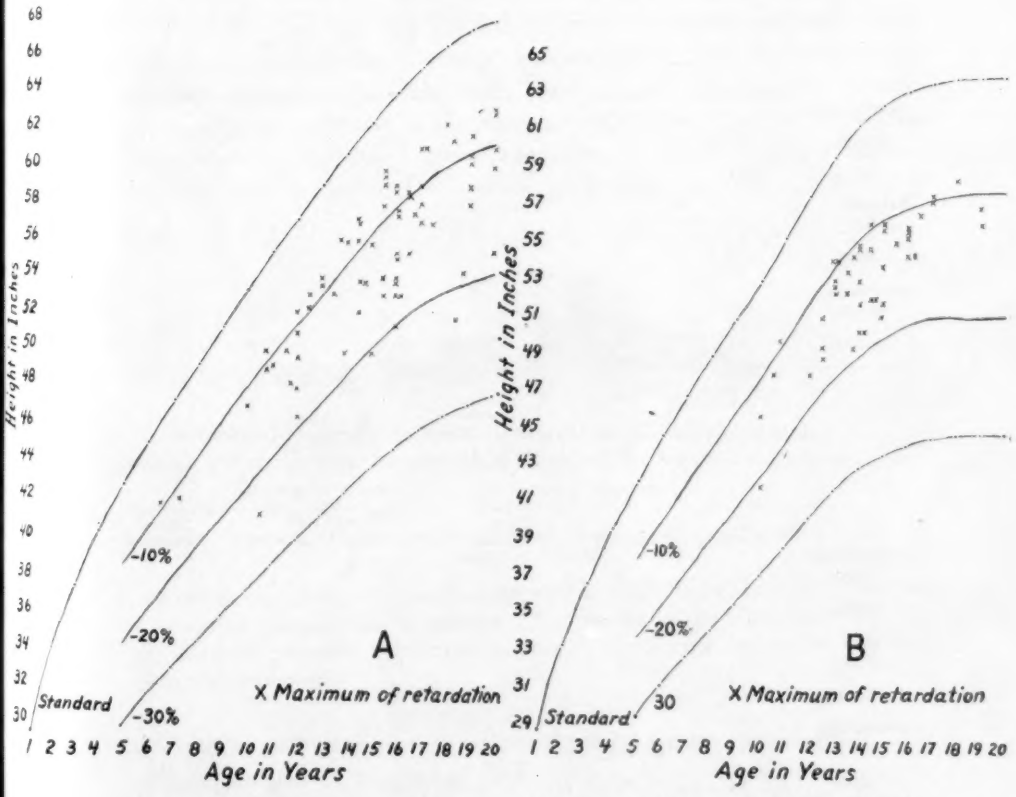

Chart 4.—Height-age relationship (*A*) for 70 retarded diabetic boys (Engelbach's standard) and (*B*) for 43 retarded diabetic girls (Engelbach's standard).

The leanness lasts longer and is more marked in boys than in girls. The greater incidence of high degrees of obesity among the girls may be something like an accentuated period of third filling (after the development of maturity).

Most of the boys have their maximal retardation in the sixteenth year, while the girls have their points of culmination in the fourteenth year, suggesting that the time of puberty is particularly prone to retardation of growth. This is the time of increasing activity of the endocrine

glands concerned with growth and development, namely, the adrenal cortex, the anterior lobe of the pituitary, the thyroid and the gonads. This theory seems tenable if one compares the time interrelation between underheight and overweight. It can be shown that the maximal incidence of obesity coincides exactly with the age of maximal retardation of height and is shifted to the left with the girls (chart 5).

TABLE 8.—*Deviations of Weight at Onset of Retardation*

	46 Boys			42 Girls		
	Percentage	Number	Total Percentage	Percentage	Number	Total Percentage
Underweight						
>20%	8.7	4	23.9	4.8	2	31.0
10-20%	15.2	7		26.2	11	
Normal						
— 0-10%	43.5	20	67.4	9.5	4	42.8
0	6.5	3		7.1	3	
+ 0-10%	17.4	8		26.2	11	
Overweight						
10-20%	8.7	4	8.7	14.3	6	26.2
>20%	0	0		11.9	5	

TABLE 9.—*Deviations of Weight at Time of Maximal Retardation*

	69 Boys			43 Girls		
	Percentage	Number	Total Percentage	Percentage	Number	Total Percentage
Underweight						
>20%	4.4	3	13.1	0	0	2.3
10-20%	8.7	6		2.3	1	
Normal						
— 0-10%	26.1	18	60.6	18.6	8	53.5
0	7.2	5		4.7	2	
+ 0-10%	36.3	25		30.2	13	
Overweight						
10-20%	15.9	11	17.3	16.7	7	44.2
>20%	1.4	1		27.8	12	

Data concerning the stature of the parents and the siblings, although incomplete, indicate that there was no hereditary lack of potentiality for growth. Of the total of 118 cases, data were available in 81. In 51 instances exact measurements for fathers, mothers and siblings were recorded. In the rest of the cases the estimation of the stature is based on memory. In only 4 cases was the father's height below 64 inches (163 cm.); in 2 the mother's height was below 60 inches (152 cm.). Ten fathers and seven mothers were classified as small (from memory). Only a single sibling was under his expected height, and in 1 case

the maternal grandmother, who had diabetes, measured 58 inches (147 cm.). Thirty per cent of the patients, including all in whose cases data were based on memory, had a family history of other small members. This evidence is not sufficient to warrant the claim that a familial trend toward a small stature alone was responsible for the retardation of the children involved, particularly since their siblings were all normal.

CLINICAL PICTURE: PECULIARITIES AND COMPLICATIONS

The following data are considered most important clinically: body measurements and deviations at certain points of the observation, proportions expressed by the stem index, sexual development, osseous age, results of metabolic studies and complications. In this section all the patients are considered as one homogenous group, as if their dwarfism had the same underlying cause. It is possible to decide whether a

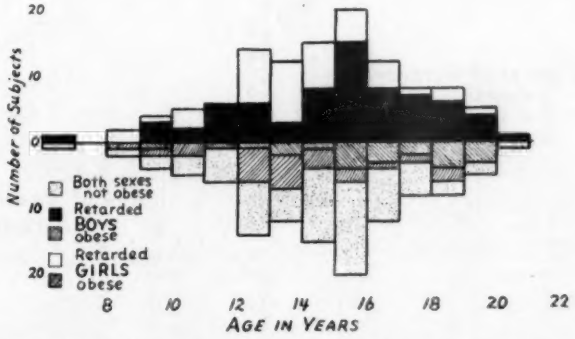

Chart 5.—Relation of maximal retardation of height to incidence of obesity for 113 retarded juvenile diabetic patients. The portion of the chart above the zero line represents maximal retardation of height; the portion below the zero line, the incidence of obesity.

subdivision and classification within the total group can be made only after an analysis of all clinical data.

The age at onset of diabetes in our particular group of retarded diabetic boys has two definite peaks, one in the sixth year and the second in the eleventh year (chart 6 *A*). The second peak occurs earlier in this group than we are accustomed to find it in large groups of diabetic boys, where it appears in the thirteenth and fourteenth years. There is a single peak in the fourth year on the girls' chart (chart 6 *B*). Many of the girls who were subsequently retarded had the onset of their diabetes between 1 and 5 years of age (chart 6 *B*). We should not be surprised that the onset of diabetes is earlier in the group of retarded children, since the diabetes can exhibit a definite influence on growth only as long as there is a certain potential of growth present.

The diabetic child is most susceptible to retardation from the twelfth to the sixteenth year of life and from the second to the sixth year of diabetes. This can be observed in chart 7 *A*, a spot map for the boys in whose cases the time of onset of retardation was known. Patients retarded when first seen were not included. In this chart the relations between the age of onset of retardation and the duration of diabetes at that time are plotted. In addition to the age period from

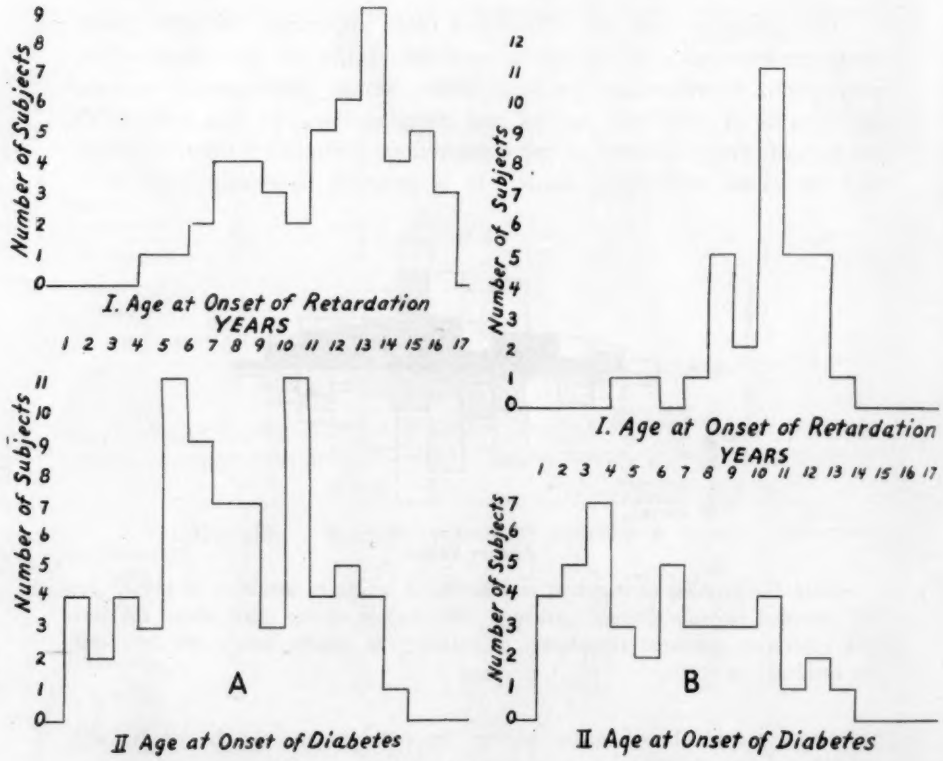
Number of Subjects
I. Age at Onset of Retardation
YEARS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Number of Subjects
I. Age at Onset of Retardation
YEARS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Number of Subjects
A
II Age at Onset of Diabetes
Number of Subjects
B
II Age at Onset of Diabetes

Chart 6.—*A*, data for retarded diabetic boys; *B*, for retarded diabetic girls. In *A*, graph *I* shows the age at onset of retardation of 49 boys and graph *II* the age at onset of diabetes of 75 boys. In *B*, graph *I* shows the age at onset of retardation of 32 girls and graph *II* the age at onset of diabetes of 43 girls.

12 to 16 years, there may be another maximum in the ninth and tenth years with duration of diabetes remaining the same, but the number of cases is too small for definite conclusions. One is inclined to attribute the ages of the two maxima to the two peaks previously mentioned. The peak between 12 and 16 years in chart 7 *A* seems to correspond to the onset incidence age of 10 to 11 years in chart 6 *A*, while the maximum in the ninth and tenth years (chart 7 *A*) would

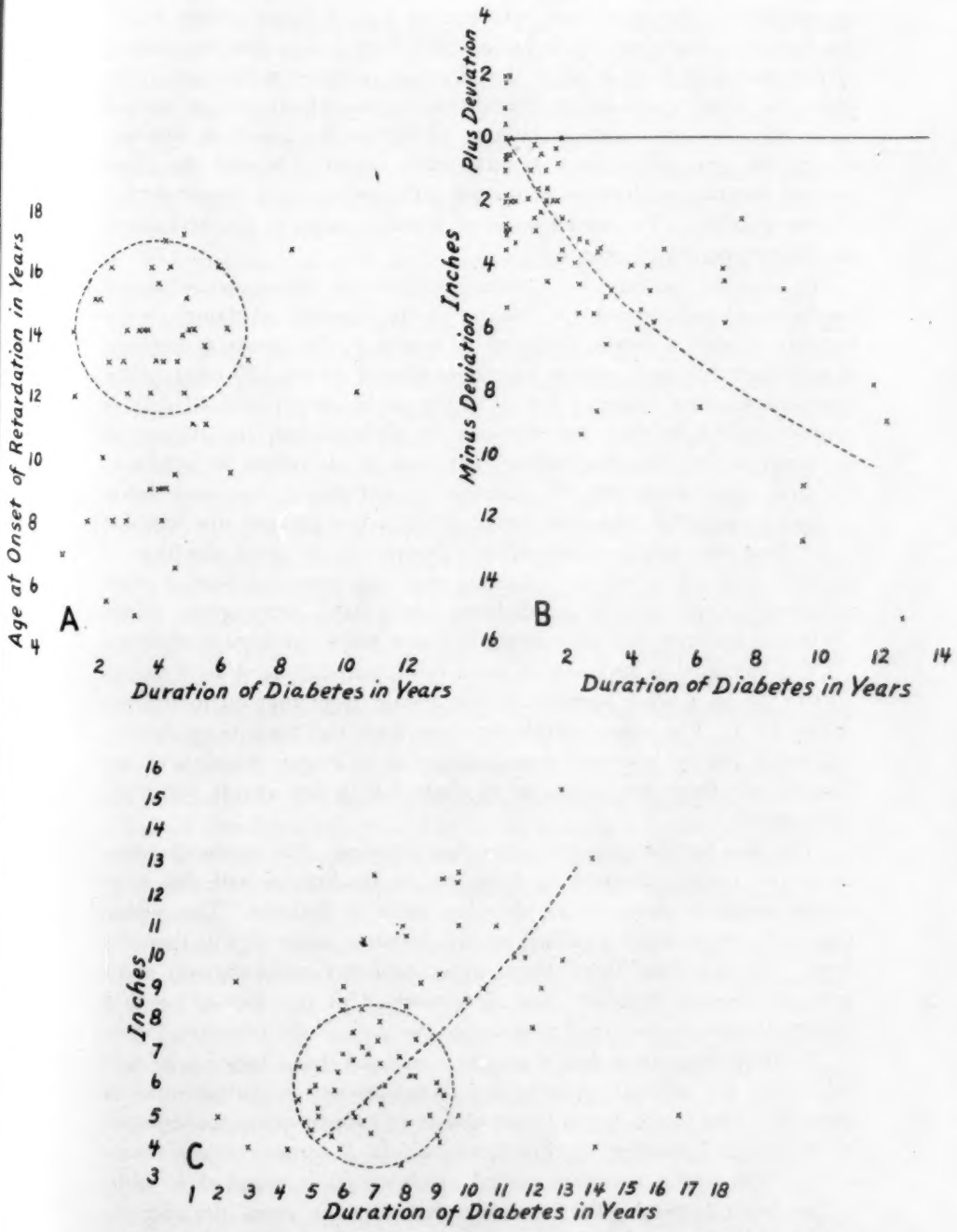

Chart 7.—*A*, duration of diabetes and age at onset of retardation of 49 boys. *B*, duration of diabetes and deviation of height at first observation of 75 boys (Engelbach's standard). *C*, maximal minus deviation and duration of diabetes at that time for 73 boys (Engelbach's standard).

correspond to the onset age incidence of 5 to 6 years (chart 6 *A*). Another fact which can be deduced from chart 7 *A* is that the danger of retardation in boys is slight if it has not occurred within six years after the onset of diabetes. Retardation in most girls has an earlier onset than in boys, perhaps because of the earlier onset of diabetes among the girls. The onset of retardation occurred beyond the sixth year of duration of diabetes in several girls, indicating a longer period of susceptibility. The earlier onset of diabetes seems to counterbalance the shorter period of growth.

In most of the retarded diabetic children the minus deviations of height developed during the course of the disease. Although some patients showed a minus deviation in height at the onset of diabetes, it was slight. Only 1 patient was more than 4 inches (10 cm.) below standard at onset (chart 7 *B*). On the whole there exists a certain proportionality between the duration of diabetes and the degree of deviation at the first observation. The data on deviations in height at the first observation and the duration of diabetes at that time bring to light three other important facts: First, a few patients are retarded more than one would expect after a comparatively short duration of diabetes; second, a few are retarded less than expected after a comparatively long duration of diabetes, and, third, very gross minus deviations are seen only after more than nine years' duration of diabetes.

The maximal retardation in most boys varied from 4 to 8 inches (10 to 20 cm.) after duration of the disease from four to nine years (chart 7 *C*). The points outside the circle show that there is an increasing trend toward maximal retardation with a longer duration of the disease, but there are again, as in chart 7 *B*, a few points which do not conform.

The data for the girls are somewhat different. The maximal minus deviation, ranging from 4 to 8 inches, is reached in half the cases within seven to eleven years after the onset of diabetes. This means that girls obtain their maximal minus deviation more slowly than the boys. On the other hand, there were absolutely and relatively more girls who became retarded soon after onset. This is important since it apparently indicates a rapid response of the girls to the retarding factor.

From the preceding data it may be concluded that a factor is present inhibiting the normal growth and development of certain diabetic children. This factor seems to act almost in proportion to the duration of diabetes. Exposure to this factor within a certain period of the disease and within a certain period of childhood is essential in order to produce this result. We have seen that after six years' duration the boys usually escape this damage entirely.

Two peaks in age at onset of retardation in boys are observed (chart 6 *A*, I). They occur in the ninth and in the fourteenth year.

It is interesting to compare graphs I and II in chart 6*A*. The peak occurring in the eighth and ninth years in graph I is postponed in time relationship to the peak occurring in the sixth year in graph II. This is true also for the two later peaks (fourteenth year in graph I and eleventh year in graph II). This time postponement represents, so to speak, the incubation time of retardation. That the two charts are not entirely congruent may be explained by the fact that a dissimilar number of cases was used.

The peaks in age at onset of retardation in girls occur in the ninth and in the eleventh year (chart 6*B*, I). The smaller peak may be only a precursor of the greater peak, so that the time between the eighth and the eleventh year can be considered as one uniform period. The peak in graph I of chart 6*B* is definitely anticipatory to the corresponding one in the boys' graph (graph I in chart 6*A*). This is to be expected since the onset peak in chart 6*B*, II precedes that of the boys, chart 6*A* II. The earlier incidence of the maximum of retardation of the girls is to be expected, since they show an earlier onset of retardation. The explanation is given in a previous section (page 688).

A consideration of the proportions of the children is very important. The span which equals the body length was measured in a few cases, and no variations from the normal were noted. The stem index (100 times sitting height over standing height) was recorded for 22 boys and 15 girls. Measurements taken after the sixteenth year of life for 12 boys showed that most of these children approached the expectation, with a slight tendency to the persistence of infantile proportions. Prior to the sixteenth year 7 of the boys were infantile in their proportions and 3 eunuchoid. The latter group was studied just before the beginning of sexual development, a period of life in which a relative eunuchoidism is characteristic. Treatment with anterior pituitary extract containing the growth hormone led to normalization of the proportions in 2 of the 3 boys.

Fifteen girls appeared more infantile than their measurements would indicate because of their short extremities. Most of the indexes recorded were below normal. The deviations were not very striking, most of them lying within the normal range of error. It must be emphasized that an anomalous behavior of the proportions depends on the time when the influencing factor begins to act. Most of the patients concerning whom data were available were between 13 and 18 years of age, that is, in a period of life in which the "physiologic infantilism" has disappeared.

Sexual development was markedly delayed in all respects. There was not a single patient with diabetic pseudodwarfism who did not show delay in sexual development at the time of maximal retardation in height. The onset of retardation in most cases occurred during the

period of sexual development (charts 6 *A*, I and 6 *B*, I). It is evident that sexual development must be involved. Sufficient clinical data, however, are not available to determine which is cause and which is effect. We are not unaware of the fact that hypogonadism may be the causative factor of retardation.

Roentgenograms of the hands and wrists were made for 39 boys and for 24 girls, in some cases repeatedly. In general they showed retardation of varying degrees. Two boys showed osseous development slightly above the expectation, and the osseous and the chronologic age coincided for 3. Two girls had osseous development slightly above the expectation, and for 3 the osseous and the chronologic age coincided.

Slight anomalies of the hands and wrists were observed by one of us (I. K. B.[25]). Eight of the 39 boys and 3 of the 24 girls for whom roentgenograms were made had pseudoepiphyses of the second metacarpals. Other deviations, less frequently observed, were pseudoepiphyses of the phalanges, slight lateral tilting of the terminal phalanges of the fifth fingers, bridged ulnar epiphyses and fusions of two carpals. One girl showed a condition resembling achondroplasia with extra ossicles in the hands and malformed short fingers. Another girl had peculiar budding of the tarsal bones and multiple centers of ossification in several carpal bones. These deviations have the same significance as the other anomalies discussed in the first section, page 680.

Basal metabolic tests were done on 35 boys (42 tests) and on 16 girls (23 tests). Most of the children showed greatly increased metabolic rates, a fact not easily interpreted. Most of the metabolic investigations were carried out in a period of definite retardation. The basal metabolic rates of the boys were 8 times between 0 and + 10 per cent, 11 times between + 10 and + 20 per cent and 14 times above + 20 per cent. Twice the rate corresponded with the prediction; 4 times it was between 0 and — 10 per cent, and 3 times it was between — 10 and — 20 per cent. Six of the basal metabolic rates in the girls were between 0 and + 10 per cent, 5 between + 10 and + 20 per cent and 8 above + 20 per cent. The basal metabolic rate in 4 girls was between 0 and — 10 per cent.

It is difficult to decide on which standard the basal metabolic rates are to be based, particularly with retarded and dwarfish persons. Benedict[26] has recommended basing the metabolic rate on the body weight for boys up to the twelfth year of life (from 3 to 38 Kg.). He advised the formula for adults for boys from 12 to 20 years of age.

25. Bogan, I. K.: Hands and Wrists of the Diabetic Child, Am. J. Dis. Child. **59**:805-815 (April) 1940.

26. Benedict, F. G.: Energy Requirements of Children from Birth to Puberty, Boston M. & S. J. **181**:107-139 (July 31) 1919; Angewandte chemische und physikalische Methoden, in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1924, vol. 4, sect. 10, pt. 3.

The basal metabolism of girls up to 12 years of age is best based on height (from 48 to 138 cm.), and that of girls between 12 and 20 years, on the predicted number of calories per kilogram of body weight according to the year of life.

TABLE 10.—*Basal Metabolic Rate*

A. Boys

Case No.	Age	Dubois-Boothby-Sandiford	Based on Weight	Combined Formula (Adult)
1	17	+13%	.....	+32.6%
2	15	±0%	.....	+16.2%
3	16	+37%	.....	+37.8%
4	11	+21%	+19.9%	.....
5	9	+31%	+39.0%	.....
	14	+3%	.....	+26.0%
6	8	+2%	+1.1%	.....
	15	−3%	.....	+5.3%
7	15	+6%	.....	+21.2%
8	12	+29%	+44.4%	.....
	17	−9%	.....	+1.7%
9	16	+20%	.....	+25.0%
	17	+13%	.....	+33.0%
10	13	−10%	.....	−5.8%
11	13	−6%	.....	+10.8%
12	11	+14%	+29.9%	.....
13	13	+15%	.....	+24.8%
14	10	+8%	+14.2%	.....
15	11	−11%	−9.8%	.....

B. Girls

Case No.	Age	Dubois-Boothby-Sandiford	Based on Height	Based on Weight	Combined Formula (Adult)
1	18	+12%	.....	+80.5%	+16.3%
2	15	+6%	.....	+48.6%	+18.3%
	16	+7%	.....	+30.4%	+9.9%
3	18	+20%	.....	+37.6%	+19.2%
4	14	+25%	.....	+72.5%	+27.0%
5	15	+6%	.....	+37.4%	+3.9%
6	10	+13%	+13.8%	.....	−4.6%
7	20	−1%	.....	+8.9%	−9.4%
8	17	−1%	.....	+34.2%	−1.2%
9	16	+26%	.....	+59.5%	+29.5%
		+10%	.....	+38.4%	+12.5%
10	13	+32%	.....	+64.9%	+27.1%
11	13	+40%	.....	+42.8%	+1.7%
12	14	+42%	.....	+84.5%	+36.9%
	15	−3%	.....	+30.2%	−3.3%
13	13	+28%	.....	+78.3%	+22.8%
		+30%	.....	+81.3%	+23.8%
14	10	+35%	+66.0%	.....	+18.8%
		+13%	+54.4%	.....	+10.5%
	11	−2%	+91.6%	.....	+45.6%
		+7%	+41.7%	.....	+7.6%

The values for the boys up to 12 years based on weight seem to correspond to the values based on the Dubois-Boothby-Sandiford method with the exception of being, on the whole, a little higher (table 10 *A*). The values calculated by the formula for adults are

uniformly higher than the values obtained by the Dubois-Boothby-Sandiford method. One would expect body weight to be a useful standard for the boys, since very few were obese.

The prediction based on height is not satisfactory for the girls (table 10 *B*). This is to be expected, since we are dealing with retarded children. Nor is the weight a valuable standard. Figures based on these standards are uniformly much higher than those according to the Dubois-Boothby-Sandiford method. The latter method and the combined formula for adults (with 3 exceptions, which we are not able to explain) give closely corresponding values.

Since we accept an increase in the basal metabolic rate in retarded diabetic children as an established fact, we must explain it. White [13] in 1932 reported elevation of the basal metabolic rate as characteristic of juvenile diabetes. Waters and Best stated that an elevation of the basal metabolic rate is characteristic of diabetes. Sundal [7] reported a high rate in a single retarded patient. One cannot explain this increase by hyperactivity of the thyroid. A possible explanation lies in our theory, already mentioned, that fatigue of the pituitary gland is preceded by a period of increased activity and that the thyrotropic factor continues to be active. To clarify this problem we investigated the specific dynamic action. This has been done with 13 subjects, 8 boys and 5 girls, after the intake of 100 to 200 Gm. of meat. The increase of metabolism was within the normal range of 25 per cent except in 1 of the children with the most characteristic dwarfism, who had a rise to 44 per cent. In no case was marked lowering of the metabolic rate observed.

The Diabetic Status.—The control of diabetes was measured by the amount of ingested sugar retained in the body, designated as "per cent control" (90 per cent control equals 90 per cent carbohydrate intake retained and 10 per cent lost). More or less simple rules concerning the diabetic situation can be established for diabetic individuals or for special groups of diabetic children, like our retarded group, on the basis of the patient's age and duration of the disease. In general, children and juveniles with long-standing diabetes can be considered as having uniformly severe diabetes.

Patients whom we have observed for many years have been subjected to different kinds of treatment in different periods. Some of them have been treated with regular insulin only and some with combined regular and protamine zinc insulin. The patients observed in the preinsulin period were treated by diet alone.

We have based our opinion of the severity of diabetes in these retarded children, first, on the comparative control in per cent, and, second, on the amount of insulin required per kilogram of body weight. In both instances we have compared the results with those obtained in

a control group of 50 patients (25 boys and 25 girls) who have had diabetes for ten years.

A few children were under constant supervision in an institution so that their diabetes was under optimal control. The other children were observed for periods of two to ten weeks at camp or periods of a week in a hospital or at office visits. The diets varied according to the year of treatment, recent diets containing 180 to 200 + Gm. of carbohydrate, adequate amounts of protein and medium amounts of fat. Since 1932 the caloric requirement has been covered in all cases according to the general rules for children (carbohydrate 40, protein 20 and fat 40 per cent of total calories).

Data were collected concerning the control of diabetes in each child. Ninety to 100 per cent control was considered as very good, 80 to 90 per cent as good and below 80 per cent as poor control. The time in years during which such data were available was totaled. The time during which adequate data were available for the boys was two hundred and twenty-eight years (an average of three years for each boy) and for the girls two hundred and sixty-three years (an average of six years for each girl). The retarded group was in very good control (90 to 100 per cent) 70 per cent of the time, in good control (80 to 90 per cent) 22 per cent of the time and in poor control only 8 per cent of the time. The children of the control group were in very good control 64 per cent of the time, in good control 28 per cent and in poor control 8 per cent. The comparison between the two groups shows, therefore, a slight predominance of very good control in favor of the retarded group. The percentage of poor control is about the same in the two groups.

Complications.—The incidence of the common complications observed in our dwarfish juvenile diabetic patients is dealt with in the following section. The control for this special purpose was represented by 50 children with poorly regulated diabetes. Children of the two sexes were considered as one unit in this analysis.

Arteriosclerosis: The most important of the degenerative complications is the change in the vascular system in response to diabetes (table 11). The incidence of arteriosclerosis in the retarded group is higher than in the control group. Arteriosclerosis was found in the eyegrounds of 14 (28 per cent) of 51 retarded diabetic children and in 6 (22 per cent) of 27 children with poorly controlled diabetes. Calcification of the vessels was present in 25 (47 per cent) of 53 retarded diabetic children and in 5 (31 per cent) of 16 children with poorly controlled diabetes.

Ocular Complications.—There was not much difference in the two groups except for the higher incidence of cataracts in the retarded group and of retinal hemorrhages in the control group (table 12).

Four children were nearly blind and 1 child totally blind. In the control group were 4 patients with impaired vision. In the retarded group 1 with each of the following ocular lesions was found: embolic atrophy of the optic nerve, lipaemia retinalis, persistent pupillary membrane, coronary cataract, lenticular opacities of congenital origin and interstitial keratitis.

Renal Lesions: Nephritis was observed in 4.2 per cent (5 patients) of 118 retarded diabetic children and in 2.0 per cent (1 patient) of 50 children with poorly controlled diabetes; nephrosis in 0.8 per cent

TABLE 11.—*Incidence of Arteriosclerosis*

	Retarded Diabetic Children (62)			Poorly Controlled Diabetic Children (29)		
	Percentage	Number	Total Percentage	Percentage	Number	Total Percentage
Roentgenograms of legs						
0	52.8	28	52.8	68.5	11	68.5
Trace	13.3	7	47.2	31.2	5	31.2
+	22.6	12				
++	11.3	6				
Eyegrounds						
0	72.5	37	72.5	77.8	21	77.8
+	27.5	14	27.5	22.2	6	22.2

TABLE 12.—*Incidence of Ocular Complications*

	Retarded Diabetic Children (72)		Poorly Controlled Diabetic Children (32)	
	Percentage	Number	Percentage	Number
Cataracts	11.1	8	6.2	2
Retinal hemorrhage	12.5	9	18.7	6
Retinitis	8.3	6	6.2	2
Iritis	2.8	2	3.1	1
Optic nerve atrophy	2.8	2	0	0
Diabetic optic neuritis	1.4	1	0	0
Retinitis proliferans	1.4	1	0	0
Normal	59.7	43	65.8	21

(1 boy) of the retarded diabetic children and in none of the control group; a large trace of albumin in 0.8 per cent (1) of the retarded children and in none of the control group. The renal function was studied in our retarded group by examining the nonprotein nitrogen and in a few cases its uric acid fraction and the phenolsulfonphthalein excretion. The average nonprotein nitrogen value (72 determinations in 48 boys and 24 girls) was 32.2 mg. per hundred cubic centimeters. The average uric acid fraction amounted to 4.4 mg. per hundred centimeters, which is normal. The average phenolsulfonphthalein excretion was 57 per cent. Therefore, the renal function was normal in the retarded group of children except for the few patients showing definite involvement of the kidneys.

Increased Blood Pressure: The blood pressure was recorded in 102 retarded children and in 47 children with poorly controlled diabetes. Of the retarded children 17.6 per cent (18) had a blood pressure above 120 mm. of mercury, and of these 5 had a value between 140 and 170. Of the children with poorly controlled diabetes 17 per cent (8) had a blood pressure above 120 millimeters of mercury, and of these 2 had a value between 140 and 150. That there is a certain tendency to elevated blood pressure in diabetic children is evident because of the relatively high incidence of arteriosclerosis, but we could discover no difference between the two groups of subjects.

Deficiency-Like Complications: One hundred and eighteen retarded diabetic children showed the following incidence of deficiency-like complications: neuritis 9.3 per cent (11 patients) and nocturnal diarrhea 3.4 per cent (4 patients). In a group of 50 children with poorly controlled diabetes the incidence was as follows: neuritis 10 per cent (5 patients) and nocturnal diarrhea 2 per cent (1 patient). No difference in the two groups is detectable.

TABLE 13.—*Incidence of Infections*

	Retarded Diabetic Children (118)		Poorly Controlled Diabetic Children (50)	
	Percentage	Number	Percentage	Number
Tuberculosis	3.4	4	2.0	1
U. T.	1.7	2	4.0	2
Infection of skin	33.0	39	24.0	12

Infections: There was a slight predominance of cutaneous infection in the retarded group (table 13). Whether this is a true expression of a lowered resistance in this particular group is difficult to say, because infection depends to a certain extent on exogenous factors. Moreover, the number of cases was not very great. It is quite conceivable, however, that a retarded group may include persons more susceptible to infection.

Caries: The incidence of both caries and pyorrhea was practically the same in the retarded group as in the 200 average diabetic patients (table 14). The retarded group showed a higher incidence of caries and pyorrhea than the poorly controlled group. This is important not only from the point of view of the retarded children; it adds further evidence for the well known fact that caries does not occur in direct proportion to the degree of the diabetic disturbance of metabolism. One sometimes finds excellent teeth in children with the most undisciplined diabetes.

Coma: The proportion of 118 retarded diabetic children having coma was 47.5 per cent (56 patients), and of 50 children with poorly con-

trolled diabetes, 80 per cent (40 patients). One would expect this predominance in a group with poorly controlled diabetes, but the incidence of nearly 50 per cent in the retarded group is high. This may be explained by the fact that 29 preinsulin patients were included and that many of the patients had not been treated with protamine insulin, which guarantees nearly complete protection against coma. Whether or not the diabetic dwarf has a truly greater susceptibility to coma is not clear.

TABLE 14.—*Condition of Teeth and Gums*

		Retarded Diabetic Children (118)			Poorly Controlled Diabetic Children (50)		
		Percentage	Number	Total Percentage	Percentage	Number	Total Percentage
No notes		....	21	....	....	10	....
Teeth	Good	52.6	51	56.7	67.5	27	70.0
	Excellent	4.1	4		2.5	1	
Caries	+	32.0	31	43.3	27.5	11	30.0
	++	11.3	11		2.5	1	
Pyorrhea	+	19.6	19	24.5	7.5	3	7.5
	++	5.2	5		0	0	

TABLE 15.—*Incidence of Enlargement of the Liver*

Degree *	Retarded Diabetic Children (114)		Poorly Controlled Diabetic Children (48)	
	Percentage	Number	Percentage	Number
0	44.7	51	54.2	26
++	26.3	30	33.3	16
+++	29.0	33	12.5	6

* +++ indicates true hepatomegaly; livers just palpable were graded at 0.

Cutaneous Complications: The cutaneous complications did not reveal any striking difference between our two groups. There were 2 children with necrobiosis lipoidica diabeticorum in the retarded group and 3 in the control group, and 1 patient with xanthoma diabeticorum in each of the two groups. The incidence of xanthosis diabetica was not studied.

Hepatomegaly: The last and most important complication is hepatomegaly, and with regard to it there was a definite difference in the two groups. The second line in table 15 (+ +) represents patients whose livers were definitely enlarged but not sufficiently to be classed as hepatomegaly. In the third line only persons with true hepatomegaly are recorded. These are the same patients who were described as having hepatomegaly in the paper of Marble, White, Bogan and Smith.[15]

Roentgenograms showed enlargement of the livers, some of which extended into the pelvis. The incidence of true hepatomegaly was two and three-tenths times as high in the retarded as in the control group.

Mortality.—Finally we wish to discuss the mortality of our retarded group. Twenty-six deaths (22.0 per cent) occurred among our 118 retarded children. There were 13 (17.3 per cent) deaths among 75 boys and 13 (30.2 per cent) among 43 girls. Pulmonary tuberculosis was the cause of death of 2 boys. Coronary occlusion, cerebral thrombosis, nephritis, cellulitis and sodium pentobarbital (soluble pentobarbital U. S. P.) poisoning each caused 1 death. The 6 remaining deaths were due to uncomplicated coma. Toxemia of pregnancy, arteriosclerosis with questionable ventricular fibrillation and lobar pneumonia each was the cause of death of 1 girl. Two girls died of pulmonary tuberculosis, making a total of 4 deaths from that disease (3.4 per cent) in this series of 118 retarded children. One girl died during an epileptic convulsion. The other 7 deaths of girls were due to diabetic coma per se. Twelve fatalities (7 boys and 5 girls) occurred in the 29 preinsulin patients (17 boys and 12 girls). If these preinsulin patients are excluded, the mortality rate is reduced to 15.7 per cent.

Laboratory Data.—Before we leave the clinical analysis of our retarded group and proceed to the discussion of the diabetic situation in these cases, a few laboratory data should be mentioned which may be of some interest and importance.

The calcium and phosphorus contents of the serum lie at the lower border of the normal range. Calcium determinations were carried out for 29 children, 11 girls and 18 boys, and phosphorus determinations for 20 children, 9 girls and 11 boys (table 16). All determinations were carried out during the time of definite retardation. The average calcium value was 10.2 mg. per hundred cubic centimeters and the average phosphorus value 3.8 mg. The lowest calcium value was 7.6 mg. per hundred cubic centimeters and the lowest phosphorus value 1.5 mg. No calcium value was above 12 mg. and only 1 phosphorus value above 5.7 mg.

The significance of the low values referred to in table 16 cannot be stated definitely. They are not pathognomonic for retardation and are probably only a rare nonobligatory accompanying sign. The values of the girl with the most characteristic diabetic pseudodwarfism were 9.7 mg. of calcium per hundred cubic centimeters and 4.8 mg. of phosphorus. The phosphatase value was normal, 8.98 Bodansky units. This girl had a peculiar lesion of her bones resembling the aseptic necrosis seen in such diseases as Köhler's. She was the only patient who had a definite lesion of the skeleton, and yet her calcium and phosphorus values were within the normal range. We have found nothing in the literature concerning deviations of the mineral metabolism in dwarfs except in renal

rickets, but it is quite possible that in cases in which the growth of bone is slowed the mineral salts in the circulation are at the lower limit of normal because of the lessened requirement.

The hemoglobin tests of 76 boys showed an average of 85 per cent, and 50 red cell counts, an average of 4.7 millions. The hemoglobin tests for 34 girls showed an average of 81.3 per cent and the red cell counts of 22 girls an average of 4.7 millions.

Tests of liver function (van den Bergh) were carried out on so few patients that the average of the values is not reliable, but we know from previous examinations (Marble, White, Bogan and Smith [15]) that the commonly adopted tests of liver function give normal results in diabetic

TABLE 16.—*Serum Calcium and Phosphorus Values*

	Boys (18)			Girls (11)	
Calcium (mg. per 100 cc.)	12.0	10.0	9.5	7.8*	10.6
	9.8	10.0	10.5	9.6	10.1
	10.8	10.4	10.2	10.7	9.7
	11.2	11.1	11.1	8.1	9.6
	10.2	10.3	10.7	9.8	
	11.2	10.1	11.0	10.8	
	10.0	10.3	10.2	9.5	
	9.7	10.6	9.6	10.6	
	10.7	9.8		9.4	
	Boys (10)			Girls (9)	
Phosphorus (mg. per 100 cc.)	5.7	4.0	3.2	4.6	4.3
	1.5†	3.7	3.6	4.4	3.4
	4.3	4.4	3.8	3.8	4.8
	3.4	3.3		3.9	3.4
	4.3	2.0‡		2.9§	

* Calcium 7.8 mg. per 100 cc.; typical diabetic dwarf; —11 inches (28 cm.); neuritis; pyorrhea.

† Phosphorus 1.5 mg. per 100 cc. at summit of retardation; typical diabetic dwarf.

‡ Phosphorus 2.0 mg. per 100 cc. at onset of retardation; Friedreich's disease (?); diabetic cataracts.

§ Phosphorus 2.9 mg. per 100 cc.; typical diabetic dwarf; —8 inches (20.3 cm.); frequent coma; death in coma (?).

hepatomegaly. Perhaps other tests (such as determination of glycogen content of the blood, diastase in blood and urine, water excretion and vitamin A tolerance) may lead to a better understanding.

Intelligence tests, carried out on many of the retarded diabetic children, showed a good average standard. The range was between 65 and 130.

The follicle-stimulating gonadotropic hormone was determined in the serum of 16 of the retarded children. The concentration was abnormally high in 2, and the hormone was not present in 14.

SUMMARY AND CONCLUSIONS

One hundred and eighteen retarded diabetic children, 75 boys and 43 girls, were analyzed.

Patients who were 4 inches (10 cm.) or more below average height for their age were included. The retardation in most of the cases

amounted to 10 to 20 per cent. A few showed a retardation of more than 20 per cent.

The height-weight relation shows that many patients moderately underweight at the onset of retardation became obese during the period of observation.

Maximal retardation coincides with maximal obesity.

The time of pubescence seems to be particularly susceptible to retardation. Girls reach the maximum of their retardation earlier than boys.

It is probable that retardation is linked with the diabetic predisposition or mechanism. A familial predisposition to small stature alone cannot be responsible for the retardation of diabetic children.

The age incidence of the onset of diabetes shows two peaks in the boys, one in the sixth year and a second one in the eleventh year. The girls show a single peak, in the sixth year.

Among boys, those from 12 to 16 years of age with a duration of diabetes of from two to six years are most apt to become retarded. Retardation has an earlier age onset in girls than in boys but occurs later in the course of diabetes, that is, after the sixth year. The danger of retardation in boys is very small if it has not occurred within six years after the onset of diabetes. The onset of retardation occurred after the sixth year of diabetes in 13 girls. Retardation occurs more frequently at a time when the growth-controlling glands are particularly easily involved.

A few of the retarded patients showed a relatively slight minus deviation at the onset of diabetes; only 1 had a deviation of more than minus 4 inches (10 cm.). Very gross minus deviations are seen only after nine years' or more duration of diabetes.

The maximal retardation in most of the boys varied from 4 to 8 inches (10 to 20 cm.) after a duration of diabetes of four to nine years. In half of the girls the maximal minus deviation, ranging from 4 to 8 inches, is reached within seven to eleven years' duration of diabetes.

There must be a factor present inhibiting the normal growth and development of certain diabetic children. This seems to act almost proportionately to the duration of the disease, but it acts only when the patient is exposed to the factor within a certain time limit of the duration of the disease and in a certain period of childhood.

The duration of diabetes at the time of retardation is not the only limiting factor for the maximal minus deviation eventually obtained.

The two peaks of onset of retardation in the boys are postponed in time relationship to the two peaks of onset of diabetes. The single peak of onset of retardation in the girls is postponed in the same manner.

The proportions of most of the children involved were infantile.

The maximal delay in sexual development occurred at the summit of retardation. Prognosis in this respect is good.

Roentgenograms of the hands and wrists disclosed a marked delay in osseous differentiation. Slight developmental anomalies, such as pseudoepiphyses and ulnar bridges, were observed in 16 of the 63 children for whom roentgenograms were made.

The basal metabolism in the majority of children having tests done was increased. The specific dynamic action was normal.

The control of diabetes of the retarded children was good. They had excellent control (90 to 100 per cent) 70 per cent of the time, good control (80 to 90 per cent) 23 per cent of the time and poor control only 8 per cent.

Hepatomegaly was the most commonly observed complication. It was two and five-tenths times as frequent in retarded children as in a group of children of normal stature with poorly controlled diabetes. With this exception there was in the retarded group only a slight predominance of cataracts, cutaneous infections, caries and pyorrhea, and a higher mortality. This may indicate a greater susceptibility to endogenous and exogenous damage not specific for diabetic pseudodwarfism but also seen in other forms of dwarfism.

Low serum phosphorus values were found in 3 of 17 patients for whom determinations were made. Low serum calcium values were present in 2 of 11 girls (8.1 and 7.8 mg. per hundred cubic centimeters).

The intelligence quotients ranged from 65 to 130.

III. CLASSIFICATION AND ETIOLOGY OF DIABETIC DWARFISM

In the previous sections we have considered all the patients more or less as one clinical unit. The uniting tie in these diabetic children has been the symptom of retardation.

The various forms of disturbance of growth (minus deviations), differentiation and development may be classified as follows:

I. Endogenous causes

A. Constitutional

1. Transitory infantilism and the temporary dysharmonies of the developmental period
2. Constitutional "miniature types"—sporadic and familial

B. Endocrinologically conditioned

1. Hypogonadism
2. Hypothyroidism
3. Hypopituitarism
4. Pubertas praecox

C. Miscellaneous: chondrodystrophy, osteogenesis imperfecta, mongolian idiocy and other forms of multiple deviations, etc.

II. Exogenous causes and specific lesions with retardation

A. Diseases of certain special organs and organ systems

1. Cardiac infantilism
2. Intestinal infantilism (celiac disease)
3. Hepatic infantilism (glycogen storage disease, von Gierke)
4. Insular infantilism
5. Renal infantilism

B. General causes:

1. Prematurity of highest degrees
2. Quantitative and qualitative nutritional diseases, e. g., xerophthalmia and rickets
3. Chronic infectious diseases, such as tertiary syphilis

One should separate growth proper from differentiation. The thyroid, thymus and pituitary are the organs of growth proper, whereas the gonads, the adrenals and the pineal body are concerned primarily, but not exclusively, with the maturing process. Before we proceed to the analysis of our own material, it may be worth while to summarize the more important clinical forms of retardation of growth and development.

Transitory infantilism (IAl), an abnormal prolongation of a transient developmental period, shows the following signs: (1) the somatic characteristics of childhood, mainly a slow rate of growth with prolonged duration and persistence of infantile body proportions; (2) retardation of the somatic sexual characteristics; (3) a retarded osseous age; (4) mentality normal and psyche infantile, and occasionally (5) a prolonged period of prepubertal obesity, often mistaken for Fröhlich's syndrome. The symptoms of this genuine infantilism are less marked in the female. The diagnosis is sometimes difficult on a single examination, but observation over a period of years shows that retardation is corrected spontaneously. This marked tendency toward self-correction is perhaps one of the most striking features of this condition. Determinations of follicle-stimulating gonadotropic hormone and of 17-keto steroids have not been made. Ovulation is delayed.

Small but otherwise normally developed children with proportions corresponding to their ages are classified as "miniature" or constitutional types. Their form of retardation is usually designated as essential microsomia in the literature concerned with adults and as hypoplasia in the pediatric literature. Only a few of these patients ever approach normal stature or weight. The rate of growth is slow and the duration normal. In contrast to the retarded osseous age in transitory infantilism and other forms of dwarfism, the differentiation in this instance cor-

responds to the chronologic age. Mentally and psychically the children are normal. The concentrations of follicle-stimulating gonadotropic hormone and of 17-keto steroids are normal.

Endocrinologically conditioned disturbances of growth constitute the second subdivision of our first group (IB). Myxedema is rare in diabetes. Considerable emphasis must be placed on dysfunction of the gonads and on hypopituitarism, since our data show that the "diabetic dwarfs" resemble in most instances the hypopituitary dwarfs. Further studies may reveal a hypogonad-like dwarf.[27] We have never observed among diabetic children the various forms of precocious puberty due to a lesion of the pineal body, adrenal cortex or ovary.

Hypopituitary dwarfism is characterized by failure of development of the genital organs at puberty. The genitalia not only fail to develop but atrophy in exact proportion to the severity of the process. It is this characteristic which distinguishes the hypopituitary dwarf from the infantile and thyroid dwarfs and the cretin, who are retarded sexually to a lesser degree. Obesity of the Fröhlich type or cachexia of the Simmonds type may be present, according to some authorities. According to others, cachexia is always present and obesity never present. Hypopituitary dwarfs are rarely mentally retarded but are psychically infantile. The concentrations of follicle-stimulating hormone and of 17-keto steroids are low. The hypogonad type resembles pure hypopituitary dwarfism except for the presence of normal strength and weight and of an excess of follicle-stimulating gonadotropin.[27]

Hepatic, insular and renal infantilism are of interest in group IIA. Hepatic infantilism (IIA3), first described by Lerebouillet,[28] is characterized by an enormously enlarged liver. This was later recognized as glycogen storage disease. The body proportions are usually infantile because of the early onset of the disturbance. The rate of growth is slow. These children are retarded mentally and psychically. Glycogen storage disease seems to represent a specific form of disturbance of hepatic function leading to dwarfism as specific as intestinal or cardiac infantilism. It may be emphasized that in 1 case true diabetes ultimately developed (Wagner and Parnas[29]). Perhaps the normal behavior of the carbohydrate function of the liver is important in guaranteeing the normal course of growth or the withdrawal of protein by the formation of sugar removes the normal source of nitrogen necessary for growth.

27. Fraser, R. W., and others: Colorimetric Assay of Seventeen Ketosteroids in Urine, J. Clin. Endocrinol. **1**:234-256 (March) 1941.

28. Lerebouillet, P.: Sur un cas de cirrhose biliaire anictérique, Bull. Soc. de pédiat. de Paris **3**:89-107, 1901.

29. Wagner, R., and Parnas, J. K.: Ueber eine eigenartige Störung des Kohlenhydratstoffwechsels und ihre Beziehungen zum Diabetes mellitus, Ztschr. f. exper. Med. **25**:361-384, 1921.

The next question to be answered is whether insular infantilism (IIA4) [30] exists. In other words, are we entitled to consider diabetes mellitus as an etiologic factor in the problem of retardation so that this form can be compared with other forms of infantilism due to diseases of special organs and organ systems? It is true that certain retarded diabetic children show symptoms which many students of diabetes attribute to neglect of the disease.

Growth and nutrition (IIB2) are intimately related. The famous metabolic studies of Rubner and Heubner prove, however, that growth in the child is guaranteed by small amounts of protein. Caloric undernutrition apparently becomes manifest in the function of growth only when the deposits of fat, carbohydrate and protein are exhausted. Skeletal growth goes on with marked underbalance if it is maintained at the cost of body material, but other structures, such as endocrine glands, suffer more. Eventually a vicious cycle is set up and growth suffers.

One must distinguish carefully between a general caloric undernutrition and the withdrawal of single foods particularly necessary for the growth of certain tissues. The significance of this partial starvation has been investigated only in regard to the skeleton and even in this respect incompletely, but it is quite clear that some retardation of growth of other organs, for instance, of the sexual organs, occurs on the basis of partial starvation. Clinical evidence of gross deficiency disease was not observed in our group. But quantitative (caloric) undernutrition will have to be considered, particularly for patients of the preinsulin era. Chronic undernutrition impedes first of all increase in weight and later increase in height as well. The impulse of growth is maintained in spite of undernutrition. With sufficient intake and assimilation of food, growth starts again. The possibility of reparation depends on the degree and duration of the disturbance and the age at which it occurs. During infancy as well as in later childhood, long-standing undernutrition leads to retardation of growth in height, a fact observed in the mass experiment of the World War. The children with quantitative undernutrition are mentally and psychically normal.

In speaking of insular infantilism we refer here only to the question as to whether or not the secondary consequences of decompensated diabetes in themselves can lead to retardation. It makes some difference whether one has to deal with quantitative undernutrition as seen in the preinsulin era or with continuously decompensated diabetes as seen in diet breakers and those patients who have an inadequate insulin supply with a sufficient caloric intake. The first condition, quantitative under-

30. This term was first used by R. Priesel (Insulärer Infantilismus mit schwerer Alveolarpyorrhöe, Wien. med. Wchnschr. **16**:437-438 [April 13] 1935). J. Fliederbaum (Infantilismus insulogenes, Warszaw. czasop. lek. **7**:1021-1045, 1930) called this condition infantilismus insulogenes.

TABLE 17.—*Data on Retarded Diabetic Girls*

HYPOPITUITARY-LIKE GIRLS

Serial No.		Age, Years	Duration, Years	Deviation of: Height, Inches	Deviation of: Weight, Pounds	Clinical Peculiarities	Therapy for Retardation	Progress
1	First observation	5.2	2.0	N	— 6.0	Preinsulin (3 yr.); enlarged liver		
	Onset of retardation	9.0						
	Maximal retardation	14.5		— 7.4				
	Last observation	17.7		— 4.0	+ 5.0			
2	First observation	9.5	3.3	— 0.8	—29.0	Preinsulin (3.2 yr.); first treated by undernutrition; hepatomegaly; blood pressure 170/100 at 17 yr.; pyelitis at 14 yr.; pubic and axillary hair and breast development at 16 yr.		
	Onset of retardation	11.0						
	Maximal retardation	14.5		—10.1				
	Last observation	19.0		— 5.0	+22.0			
3	First observation	7.2	1.8	— 3.8	—14.0	Preinsulin (1.8 yr.); undernutrition; starvation diet for long period during insulin treatment; at 17 yr. considerably underdeveloped; no menses		Fairly good period of growth
	Onset of retardation	8.0						
	Maximal retardation	12.5		— 9.1				
	Last observation	25.8		— 4.5	+19.0			
4	First observation	6.9	1.0	+ 3.0	—15.0	Hepatomegaly; arteriosclerosis; severe neuritis; at 20 yr. no menses; late breast developement; no axillary hair		Missed pubertal spurt of growth
	Onset of retardation	12.0						
	Maximal retardation	15.0		— 6.5				
	Last observation	24.0		— 1.5	—14.0			
5	First observation	12.0	5.2	— 6.5	—10.0	Preinsulin (0.6 yr.); lived on free diet; frequent coma; highest blood sugar value 900 mg. per 100 cc., walked into office with this blood sugar concentration; hepatomegaly; arteriosclerosis; tuberculosis; retinal hemorrhages; nephrosis; neuritis; breast development at 17 yr.; very little development at 19 yr.; menarche (but only 1 period per year); severe pyorrhea		Death from pulmonary tuberculosis
	Onset of retardation	....						
	Maximal retardation	16.0		— 8.9				
	Last observation	22.7		— 5.5	—10.0			
6	First observation	10.5	8.3	— 8.0	—10.0	Preinsulin (2.3 yr.); short observation; epilepsy		Death from epileptic convulsion
	Onset of retardation	....						
	Maximal retardation	12.0		— 9.6				
	Last observation	20.8		— 9.0	+20.0			
7	First observation	16.5	8.3	— 6.9	+26.0	Hepatomegaly; menarche at 16 yr.		Death in coma
	Onset of retardation	....						
	Maximal retardation	16.5		— 6.9				
	Last observation	16.5		— 6.9	+26.0			
8	First observation	19.0	9.6	— 9.0	— 5.0	Pus in urine at 20 yr.; appendectomy (appendix normal, tabes mesenterica); arteriosclerosis; retinitis; cataracts; noctural diarrhea; hepatomegaly; breasts undeveloped, no axillary hair, no menses at 19 yr.	Thyroid	Death in coma
	Onset of retardation	....						
	Maximal retardation	19.0		— 9.0				
	Last observation	20.1		— 8.0	—13.0			
9	First observation	9.2	2.3	— 2.0	— 8.0	Preinsulin (2.3 yr.); hepatomegaly; arteriosclerosis; neuritis; diarrhea; pubic and axillary hair at 14 yr.; menses at 17 yr.	Anterior pituitary extract and thyroid (very late)	Married; one child
	Onset of retardation	10.0						
	Maximal retardation	14.5		—10.1				
	Last observation	27.1		— 6.0	—19.0			
10	First observation	3.6	0.5	— 1.0	— 3.0	Obesity; breast development and beginning axillary hair at 14 yr.; menses at 16 yr.; hepatomegaly	Little anterior pituitary extract and thyroid	
	Onset of retardation	10.0						
	Maximal retardation	13.0		— 7.3				
	Last observation	19.9		— 4.5	+19.0			

11	First observation.....	8.2	0.5	+ 1.0	+ 2.0	Hepatomegaly; beginning obesity; no breast-development, no menses at 15 yr.	Anterior pituitary extract (very little treatment) and thyroid	.....
	Onset of retardation.....	12.0						
	Maximal retardation.....	16.0		— 7.9				
	Last observation.....	16.0		— 7.9	+ 5.0			
12	First observation.....	11.7	7.0	— 6.0	+ 1.0	Preinsulin (2.3 yr.); epilepsy; hepatomegaly; pyorrhea; breast development, pubic hair, little axillary hair, menarche at 18 yr.	Anterior pituitary extract and thyroid	.....
	Onset of retardation.....	....						
	Maximal retardation.....	15.0		— 8.7				
	Last observation.....	21.4		— 2.8	+ 2.0			
13	First observation.....	9.4	2.9	— 4.0	N	Hepatomegaly (treatment with betaine).....	Anterior pituitary extract and thyroid	Good response to treatment; grew well after omission of anterior pituitary extract
	Onset of retardation.....	11.0						
	Maximal retardation.....	13.5		— 8.3				
	Last observation.....	15.4		— 1.5	—32.0			
14	First observation.....	12.1	9.9	—10.3	—10.0	Preinsulin (0.4 yr.); retinal hemorrhages, slight retinal sclerosis; hepatomegaly; breast development; pubic and axillary hair; menarche at 18 yr.	Anterior pituitary extract and thyroid	Good response to treatment
	Onset of retardation.....	....						
	Maximal retardation.....	14.0		—11.1				
	Last observation.....	19.4		— 6.3	— 2.0			
15	First observation.....	12.7	6.3	—10.0	+ 6.5	Hepatomegaly (treated with betaine); axillary hair and breast development at 17 yr.; menarche at 12 yr. for 3 mo.; no menses at 17 yr.; epilepsy	Anterior pituitary extract and thyroid	Excellent response to treatment
	Onset of retardation.....	....						
	Maximal retardation.....	15.0		—10.7				
	Last observation.....	18.7		— 2.5	—14.0			
16	First observation.....	13.0	9.0	— 6.9	+ 2.0	Large liver; menarche at 15 yr.	Anterior pituitary extract and thyroid	Good response to treatment
	Onset of retardation.....	....						
	Maximal retardation.....	13.0		— 6.9				
	Last observation.....	19.8		— 3.0	+10.0			
17	First observation.....	12.3	2.3	— 4.3	—15.0	Poor control; hepatomegaly	Anterior pituitary extract and thyroid (short period of treatment)	.....
	Onset of retardation.....	....						
	Maximal retardation.....	14.5		— 6.1				
	Last observation.....	19.6		— 2.0	N			
18	First observation.....	10.5	8.1	— 5.0	+ 2.0	Enlarged liver; development good, perhaps even a little advanced; menses at 15 yr.	Anterior pituitary extract and thyroid	Very good response to anterior pituitary extract
	Onset of retardation.....	....						
	Maximal retardation.....	13.8		— 6.9				
	Last observation.....	17.0		— 2.5	N			
19	First observation.....	10.0	8.5	—11.0	+ 8.5	Unique case; onset of diabetes at 1 yr.; child showed all characteristics of hypopituitary-like dwarfism; congenital anomalies and abnormal response to exogenous factors; brachycephalus, brachydactylia; peculiar lesion of bones (aseptic necrosis like Köhler's disease); calcification of adrenals; lens opacities; papillary edema; neuritis	Anterior pituitary extract and thyroid	Excellent response to anterior pituitary extract
	Onset of retardation.....	....						
	Maximal retardation.....	10.0		—11.0				
	Last observation.....	12.8		— 8.0	+24.0			
20	First observation.....	16.1	6.2	— 7.0	+ 6.8	Enlarged liver; almost no sexual development at 16 yr.	Anterior pituitary extract and thyroid	Short observation
	Onset of retardation.....	....						
	Maximal retardation.....	16.1		— 7.0				
	Last observation.....	17.7		— 6.0	—11.0			
21	First observation.....	2.3	0.2	N	— 2.0	No complications	Anterior pituitary extract and thyroid	.....
	Onset of retardation.....	8.0						
	Maximal retardation.....	15.0		—11.5				
	Last observation.....	17.3		— 9.0	— 3.0			
23	First observation.....	2.3	0.2	N	— 3.0	Arteriosclerosis (fundi); large liver; very slow development of secondary sex characteristics; no pubic or axillary hair or breast development but beginning rounding of hips at 14 yr.	Anterior pituitary extract and thyroid (practically untreated)	.....
	Onset of retardation.....	5.0						
	Maximal retardation.....	14.0		—11.0				
	Last observation.....	16.0		— 5.4	— 1.0			

TABLE 17.—*Data on Retarded Diabetic Girls—Continued*

Serial No.		Age, Years	Duration, Years	Deviation of: Height, Inches	Deviation of: Weight, Pounds	Clinical Peculiarities	Therapy for Retardation	Progress
	HYPOPITUITARY-LIKE GIRLS—Continued							
23	First observation	10.2	9.3	— 5.5	+ 8.0	Pulmonary tuberculosis; brachydactylia, clubbed thumb; hepatomegaly; axillary and pubic hair but no breast development and no menses at 14 yr. (dysharmonic development)	Anterior pituitary extract and thyroid (short period of time)	Death from pulmonary tuberculosis
	Onset of retardation	....						
	Maximal retardation	16.1		— 8.8				
	Last observation	16.1		— 8.8	+ 2.0			
	TRANSITORY INFANTILISM (GIRLS)							
24	First observation	6.3	1.9	N	— 9.0	Preinsulin (1.3 yr.); at first on Allen diet; diet breaker	.....	Good potential of growth
	Onset of retardation	8.0						
	Maximal retardation	14.0		— 6.6				
	Last observation	22.7		— 3.0	+22.0			
25	First observation	3.5	0.9	— 1.0	— 4.0	Beginning obesity; no menses at 15 yr.	.....	Good potential of growth
	Onset of retardation	10.0						
	Maximal retardation	13.0		— 5.6				
	Last observation	19.3		— 3.3	+ 6.0			
26	First observation	1.9	0.1	— 0.8	— 2.0	Large liver	.....	.....
	Onset of retardation	4.0						
	Maximal retardation	10.5		— 6.0				
	Last observation	13.5		— 5.5	N			
27	First observation	5.8	2.8	N	+ 2.0	Secondary anemia; enlarged liver; beginning development of breasts and appearance of pubic hair but no axillary hair at 14 yr.; no menarche	.....	Good potential of growth
	Onset of retardation	11.0						
	Maximal retardation	13.0		— 5.6				
	Last observation	16.0		— 3.0	— 6.0			
28	First observation	4.1	0.1	— 2.8	— 3.3	.....	.....	.....
	Onset of retardation	8.0						
	Maximal retardation	10.8		— 5.7				
	Last observation	12.8		— 5.7	+ 6.0			
29	First observation	10.7	0.4	— 5.0	— 5.0	Enlarged liver; severe neuritis; rounding of hips, breasts just beginning to develop and pubic hair but no axillary hair at 13 yr.	.....	Death in coma
	Onset of retardation	....						
	Maximal retardation	13.0		— 6.6				
	Last observation	13.0		— 6.6	— 6.0			
30	First observation	4.2	1.0	— 2.0	N	Good development at 15 yr.; menarche at 15 yr.	Anterior pituitary extract and thyroid	.....
	Onset of retardation	11.0						
	Maximal retardation	12.5		— 7.6				
	Last observation	17.7		— 3.0	— 5.0			
31	First observation	13.7	10.6	— 4.3	— 5.0	Hepatomegaly	Anterior pituitary extract and thyroid	Good potential of growth
	Onset of retardation	....						
	Maximal retardation	15.5		— 7.9				
	Last observation	16.4		— 3.0	— 2.0			
	CONSTITUTIONAL (GIRLS)							
32	First observation	10.0	1.2	— 6.0	— 6.0	Always free diet; enlarged liver; opacities in lens (congenital origin); fundi normal	.. ..	Death in coma (insulin omitted for 36 hr.)
	Onset of retardation	....						
	Maximal retardation	14.0		— 9.6				
	Last observation	17.8		— 7.5	+15.0			

33	First observation	17.0	3.3	— 6.1	+11.0	Preinsulin (0.6 yr.); first seen at 17 yr.; arteriosclerosis; retinitis proliferans, preretinal hemorrhages, total blindness; xanthoma; carbuncles; nocturnal diarrhea; achlorhydria	.....	Death in coma
	Onset of retardation	....						
	Maximal retardation	17.0		— 6.1				
	Last observation	26.7		— 3.0	+28.0			
34	First observation	12.4	1.4	— 4.5	— 6.0	Preinsulin (0.2 yr.); child almost blind in left eye from birth; complete development at 16 yr.	.....	Death from eclampsia
	Onset of retardation	....						
	Maximal retardation	14.0		— 6.5				
	Last observation	18.6		— 4.5	+ 3.0			
35	First observation	18.0	4.1	— 5.5	+ 4.0	Poor control of diabetes; despondent at times; menarche at 15 yr.	.....	Married; one baby
	Onset of retardation	....						
	Maximal retardation	18.0		— 5.5				
	Last observation	29.4		— 5.0	—22.0			
36	First observation	11.1	1.8	— 5.0	+ 7.0	Hepatomegaly; normal development; menarche at 14 yr.	.....	.....
	Onset of retardation	....						
	Maximal retardation	15.0		— 6.6				
	Last observation	16.0		— 6.5	N			
37	First observation	7.6	0.1	— 2.5	— 1.0	Frequent coma; large trace of albumin in urine; phenolsulfonphthalein excretion 48 per cent at 18 yr.	Thyroid	Married
	Onset of retardation	10.0						
	Maximal retardation	11.0		— 6.8				
	Last observation	18.6		— 3.0	+ 4.0			
38	First observation	10.2	1.2	— 3.5	— 2.0	Development complete at 14 yr.; menarche established at this age	Anterior pituitary extract and thyroid for 2 mo.	.....
	Onset of retardation	11.5						
	Maximal retardation	17.0		— 6.0				
	Last observation	19.1		— 6.0	— 4.0			
	CONGENITAL ANOMALY (GIRLS)							
39	First observation	7.0	1.8	— 4.8	— 3.0	Borderline case; multiple malformations, congenital dislocation of hips, hallux valgus, malocclusion, brachydactylia, kyphoscoliosis (hereditary); achondroplasia (roentgenologic diagnosis); breasts and pubic hair developed at 12 yr.; menarche at 13 yr.	.....	Measurements difficult to evaluate because of kyphoscoliosis
	Onset of retardation	....						
	Maximal retardation	15.7		—12.5				
	Last observation	15.7		—12.5	—37.0			
40	First observation	13.2	0.6	— 4.5	—16.0	No development at 16 yr.; feeblemindedness; oligophrenia; mongolian idiocy (?)	.....	No growth from 13 to 15 yr.; death from lobar pneumonia
	Onset of retardation	13.2						
	Maximal retardation	16.0		— 7.3				
	Last observation	16.0		— 7.3	—16.0			
	UNDERNUTRITION (GIRLS)							
41	First observation	3.7	2.2	N	+ 3.5	Preinsulin (7.9 yr.); undernutrition	.....	Death in coma
	Onset of retardation	8.0						
	Maximal retardation	9.8		— 7.0				
	Last observation	9.8		— 7.0	+ 1.0			
	TERTIARY SYPHILIS (GIRLS)							
42	First observation	12.5	2.6	— 4.5	+ 4.0	Poor control; congenital syphilis; interstitial keratitis; rounding of hips and pubic hair but no axillary hair and no menses at 14 yr.	.....	Good potential of growth; death from coma
	Onset of retardation	....						
	Maximal retardation	13.5		— 7.1				
	Last observation	14.3		— 5.8	+ 9.5			
	NEGLECT OF DIABETES (GIRLS)							
43	First observation	18.6	10.1	— 5.0	—19.0	Borderline case; poor control; coronary cataracts; marked undevelopment; little axillary hair and no menses at 18 yr.	.....	Death from coma
	Onset of retardation	....						
	Maximal retardation	18.6		— 5.0				
	Last observation	18.6		— 5.0	—19.0			

TABLE 18.—*Data on Retarded Diabetic Boys*

HYPOPITUITARY-LIKE BOYS

Serial No.		Age, Years	Duration, Years	Deviation of Height, Inches*	Deviation of Weight, Pounds	Clinical Peculiarities	Therapy for Retardation	Progress
1	First observation	9.5	1.5	— 5.0	— 6.5	Preinsulin (7.2 yr.); adequate diet		
	Onset of retardation	....						
	Maximal retardation	15.5		— 9.2				
	Last observation	20.0		— 5.0	— 4.0			
2	First observation	7.3	0.1	+ 1.0	— 8.0	Preinsulin (1.5 yr.); undernutrition and poor control; chiropractic treatment; cataracts, retinal hemorrhages, slight retinal sclerosis (1934)		Death in coma
	Onset of retardation	12.0						
	Maximal retardation	17.5		— 9.0				
	Last observation	19.5		— 9.0	—15.0			
3	First observation	13.8	2.8	— 8.0	+12.0	Preinsulin (1.4 yr.); slight undernutrition; hepatomegaly; arteriosclerosis; nephritis		Death from chronic interstitial nephritis and diabetic coma
	Onset of retardation	....						
	Maximal retardation	20.0		—12.5				
	Last observation	20.6		—12.0	+ 4.0			
4	First observation	5.5	0.1	— 0.8	— 5.0	No pubic hair at 14 yr. (first observation)		
	Onset of retardation	9.0						
	Maximal retardation	21.2		—12.0				
	Last observation	21.2		—12.0	+ 3.0			
5	First observation	10.9	0.2	— 4.0	— 9.0	One year dietetic treatment only; diabetic optic neuritis; at 15 yr. pale disks but no definite atrophy; 3 yr. later no remarkable abnormalities in visual mechanism; arteriosclerosis; pyorrhea; late development, no pubic or axillary hair at 18 yr.		Long after-growth
	Onset of retardation	13.0						
	Maximal retardation	15.0		— 6.6				
	Last observation	22.9		— 4.0	—33.0			
6	First observation	10.1	0.0	+ 0.3	+ 1.0	No special peculiarity		
	Onset of retardation	13.0						
	Maximal retardation	16.8		— 7.5				
	Last observation	16.8		— 7.5	+ 4.0			
7	First observation	11.2	2.1	— 3.0	— 7.0	Cataracts; at 15 yr. undeveloped		Death in coma
	Onset of retardation	12.0						
	Maximal retardation	14.8		— 8.0				
	Last observation	14.8		— 8.0	— 4.5			
8	First observation	9.0	0.1	+ 1.0	N	Arteriosclerosis; retinitis proliferans; retinal hemorrhages; at 16 yr. undeveloped; at 19 yr. beginning pubic but no axillary hair		Death from pulmonary tuberculosis
	Onset of retardation	14.0						
	Maximal retardation	16.0		— 6.7				
	Last observation	21.3		— 5.5	—13.0			
9	First observation	12.5	6.2	— 8.0	+ 2.0	Preinsulin (0.5 yr.); hepatomegaly; arteriosclerosis; at 14 yr. completely developed		Death from pulmonary tuberculosis
	Onset of retardation	....						
	Maximal retardation	14.0		—10.7				
	Last observation	....						
10	First observation	12.7	3.7	— 4.0	— 4.0	Borderline case; cataracts; arteriosclerosis; at 18 yr. voice changed; no axillary hair		Death from cellulitis
	Onset of retardation	....						
	Maximal retardation	18.0		— 4.5				
	Last observation	18.0		— 4.5	—20.0			

11	First observation	5.1	0.1	+ 0.5	— 4.0	Large liver		
	Onset of retardation	8.0						
	Maximal retardation	10.0		— 6.2				
	Last observation	10.0		— 6.2	— 5.0			
12	First observation	13.8	6.9	— 5.0	N	Delayed development; seen only once		
	Onset of retardation	....						
	Maximal retardation	19.6		— 7.3				
	Last observation	19.6		— 7.3	—15.0			
13	First observation	12.8	5.0	— 2.5	+ 5.0	No pubic or axillary hair at 15 yr.		
	Onset of retardation	15.0						
	Maximal retardation	15.0		— 4.3				
	Last observation	15.0		— 4.3	+ 5.0			
14	First observation	14.7	1.1	— 1.0	—18.0	Preinsulin (2.7 yr.); slight undernutrition at beginning; poorly controlled; cataracts, retinal exudate, retinal hemorrhages; arteriosclerosis, increased blood pressure; albuminuria, casts; phenolsulfonphthalein excretion 45 per cent; good sexual development		
	Onset of retardation	16.0						
	Maximal retardation	20.0		— 4.9				
	Last observation	33.2		— 4.5	—10.0			
15	First observation	5.6	0.1	N	N	Preinsulin (3.3 yr.); first undernutrition, then adequate diet; very low blood phosphorus level (1927); very late sexual development	Thyroid	Married; 2 children
	Onset of retardation	8.0						
	Maximal retardation	12.0		—10.6				
	Last observation	26.2		— 4.5	N			
16	First observation	16.5	2.1	— 4.8	— 4.0	Preinsulin (3.9 yr.); arteriosclerosis; cataracts; slight undernutrition until 1926, then adequate diet	Thyroid	
	Onset of retardation	....						
	Maximal retardation	20.0		— 7.0				
	Last observation	35.0		— 5.0	N			
17	First observation	4.8	1.5	— 2.0	—12.0	Preinsulin (4.3 yr.); first slight undernutrition, then adequate diet; completely undeveloped at 16 yr.	Thyroid	
	Onset of retardation	6.0						
	Maximal retardation	16.0		— 9.9				
	Last observation	21.5		— 6.0	— 3.0			
18	First observation	6.3	0.0	— 2.0	— 2.0	At 14 yr. not developed; at 18 yr. fully developed	Thyroid	
	Onset of retardation	8.0						
	Maximal retardation	16.0		— 8.7				
	Last observation	18.0		— 8.0	+ 9.0			
19	First observation	16.0	9.4	—11.0	+ 5.0	Preinsulin (3.0 yr.); undernutrition until 16th yr.; undeveloped at 16 yr.	Thyroid	Good response to treatment
	Onset of retardation	....						
	Maximal retardation	16.0		—11.0				
	Last observation	26.5		— 3.0	+ 2.0			
20	First observation	3.4	0.6	— 1.5	— 1.0	Hepatomegaly	Thyroid (only a short time)	Good potential of growth
	Onset of retardation	8.0						
	Maximal retardation	12.0		— 7.5				
	Last observation	14.6		— 4.5	+ 6.0			
21	First observation	16.0	12.2	— 9.0	+ 3.0	Preinsulin (1.9 yr.); undernutrition for first 10 yr. of diabetes; no complications; at 18 yr. pubic but no axillary hair; voice changed; at 22 yr. completely developed	Thyroid	
	Onset of retardation	....						
	Maximal retardation	16.0		— 9.0				
	Last observation	24.6		N	+ 4.0			
22	First observation	18.5	13.1	—15.0	— 6.0	Typical diabetic dwarf; completely undeveloped at 18 yr.	Anterior pituitary extract and thyroid (only few injections)	Seen only once
	Onset of retardation	....						
	Maximal retardation	18.5		—15.0				
	Last observation	18.5		—15.0	— 6.0			

* Adult heights taken from the Engelbach standards (male, 68 inches; female, 64 inches).

TABLE 18.—*Data on Retarded Diabetic Boys—Continued*

HYPOPITUITARY-LIKE BOYS—Continued

Serial No.		Age, Years	Duration, Years	Deviation of: Height, Inches	Deviation of: Weight, Pounds	Clinical Peculiarities	Therapy for Retardation	Progress
23	First observation	14.9	8.9	— 4.0	N	At 14.9 yr. undeveloped	Anterior pituitary extract and thyroid	Seen only once
	Onset of retardation	....						
	Maximal retardation	14.9		— 4.0				
	Last observation	14.9		— 4.0	N			
24	First observation	6.6	1.1	— 2.0	N	Preinsulin (1.6 yr.); undernutrition at beginning, later adequate diet; hepatomegaly; late development; no axillary or pubic hair at 18 yr.; at 20 yr. completely developed	Anterior pituitary extract and thyroid	Excellent response to treatment
	Onset of retardation	9.0						
	Maximal retardation	18.8		—13.1				
	Last observation	24.5		— 5.5	+12.0			
25	First observation	3.4	1.7	— 3.5	+ 2.0	At 14 yr. started to develop; developed very slowly; at 18 yr. development corresponded to 14 yr. standard	Anterior pituitary extract and thyroid	.....
	Onset of retardation	5.0						
	Maximal retardation	10.8		— 5.7				
	Last observation	18.5		— 3.0	+15.0			
26	First observation	6.4	0.9	— 3.0	N	Undeveloped at 17 yr.; arteriosclerosis	Few injections of anterior pituitary extract and thyroid	Very good response to treatment
	Onset of retardation	11.0						
	Maximal retardation	15.0		—12.4				
	Last observation	22.4		— 6.5	N			
27	First observation	9.6	1.2	N	— 5.0	Hepatomegaly; pyorrhea; arteriosclerosis (?); at 16 yr. undeveloped; at 18 yr. voice changing; at 19 yr. completely developed	Anterior pituitary extract and thyroid	Good response to treatment
	Onset of retardation	13.0						
	Maximal retardation	16.5		— 6.3				
	Last observation	21.2		— 3.6	+10.0			
28	First observation	14.5	3.1	— 5.0	+ 7.0	Hepatomegaly; arteriosclerosis; at 14 yr. undeveloped; developed at about 17 yr.	Anterior pituitary extract and thyroid for short time	.....
	Onset of retardation	....						
	Maximal retardation	19.0		— 8.5				
	Last observation	26.5		— 8.5	— 3.0			
29	First observation	10.7	0.0	— 3.5	— 7.0	Necrobiosis lipoidica diabeticorum; at 19 yr. axillary and body hair; voice changed	Anterior pituitary extract and thyroid	Epiphyses fusing when treatment started
	Onset of retardation	12.0						
	Maximal retardation	16.8		— 7.7				
	Last observation	19.0		— 6.3	+ 6.0			
30	First observation	6.2	0.1	— 4.0	— 1.0	Hepatomegaly; arteriosclerosis; completely undeveloped when treatment started; completely developed at 16 yr.	Anterior pituitary extract and thyroid	Excellent response to anterior pituitary extract
	Onset of retardation	7.0						
	Maximal retardation	11.8		— 8.7				
	Last observation	16.4		— 2.5	N			
31	First observation	8.0	0.1	— 2.5	— 2.0	Liver enlarged; at 15 yr. infantile, no pubic or axillary hair	Anterior pituitary extract and thyroid	.....
	Onset of retardation	10.0						
	Maximal retardation	15.5		—11.0				
	Last observation	17.0		— 8.5	+ 7.0			
32	First observation	6.9	3.4	— 6.0	— 4.0	Hepatomegaly; pyorrhea; hyperchlorhydria (free HCl 72.8); at 15.5 yr. pubic hair just appearing	Anterior pituitary extract and thyroid	Failure of treatment with anterior pituitary extract
	Onset of retardation	....						
	Maximal retardation	14.5		— 2.5				
	Last observation	15.8		— 8.0	+ 5.5			

33	First observation	9.7	5.6	— 4.5	— 9.0	Father had dementia paralytica; paternal grandfather a giant (?); hepatomegaly (treated with betaine); completely undeveloped at 14 yr.; at 17 yr. completely developed	Anterior pituitary extract and thyroid	Good response to anterior pituitary extract
	Onset of retardation	....						
	Maximal retardation	12.0		— 9.1				
	Last observation	19.0		— 3.0	—17.0			
34	First observation	12.3	3.1	— 6.0	+ 7.0	Cataracts; arteriosclerosis; enlarged liver (treated with betaine); very poor teeth; at 16 yr. completely undeveloped; at 19 yr. small amount of axillary hair; testes small	Anterior pituitary extract and thyroid	.....
	Onset of retardation	....						
	Maximal retardation	16.0		—12.6				
	Last observation	22.0		— 9.0	+23.0			
35	First observation	11.9	1.3	— 1.0	— 2.0	Arteriosclerosis (eyes); at 17 yr. completely undeveloped	Very little anterior pituitary extract and thyroid	.....
	Onset of retardation	14.0						
	Maximal retardation	17.0		— 8.4				
	Last observation	17.9		— 6.0	N			
36	First observation	12.7	5.0	— 5.8	— 7.0	Hepatomegaly, treated with betaine; lipaemia retinalis; undeveloped before treatment; at 17 yr. completely developed	Anterior pituitary extract and thyroid	.....
	Onset of retardation	....						
	Maximal retardation	12.7		— 5.8				
	Last observation	19.9		— 5.8	—13.0			
37	First observation	10.5	9.4	—12.7	+ 3.0	Extremely retarded; mother said he was normal at onset of diabetes; hepatomegaly; mentally retarded	Anterior pituitary extract and thyroid	Excellent response to treatment
	Onset of retardation	....						
	Maximal retardation	10.5		—12.7				
	Last observation	14.7		— 6.3	— 6.0			
38	First observation	16.5	3.1	— 9.3	— 2.0	Poorly controlled; at 17 yr. no pubic or axillary hair; at 18 yr. pubic hair developing	Very little treatment; anterior pituitary extract weekly and thyroid	Good response to treatment
	Onset of retardation	....						
	Maximal retardation	16.5		— 9.3				
	Last observation	18.9		— 6.3	+ 3.0			
39	First observation	12.9	7.0	— 5.0	+ 4.0	At 12 yr. undeveloped; completely developed at 14 yr.	Anterior pituitary extract and thyroid	Excellent response to treatment
	Onset of retardation	....						
	Maximal retardation	13.5		— 6.9				
	Last observation	14.2		— 3.5	+ 2.0			
40	First observation	14.6	11.7	— 8.5	+ 9.0	Typical diabetic dwarf; liver enlarged; at 15 yr. practically undeveloped	Anterior pituitary extract and thyroid	Excellent response to treatment
	Onset of retardation	....						
	Maximal retardation	14.6		— 8.5				
	Last observation	16.9		— 2.5	+ 6.0			
41	First observation	7.8	2.9	— 3.0	— 5.0	At beginning no insulin	Anterior pituitary extract for 3 mo.	.....
	Onset of retardation	9.0						
	Maximal retardation	15.8		—10.0				
	Last observation	15.8		—10.0	+ 3.0			
42	First observation	7.5	2.6	— 3.0	+ 8.0	Hepatomegaly; insufficient treatment with single daily dose of regular insulin for a long time	Anterior pituitary extract	Death in coma
	Onset of retardation	9.0						
	Maximal retardation	11.4		— 6.3				
	Last observation	11.4		— 6.3	+ 8.0			
	TRANSITORY INFANTILISM (BOYS)							
43	First observation	12.3	0.1	+ 0.8	—20.0	Preinsulin (2 yr.); slight undernutrition	.....	Death from cerebral thrombosis; coma
	Onset of retardation	17.0						
	Maximal retardation	18.0		— 4.5				
	Last observation	26.5		— 1.0	N			

TABLE 18.—*Data on Retarded Diabetic Boys—Continued*

TRANSITORY INFANTILISM (BOYS)—Continued

Serial No.		Age, Years	Duration, Years	Deviation of: Height, Inches	Deviation of: Weight, Pounds	Clinical Peculiarities	Therapy for Retardation	Progress
44	First observation	11.6	1.6	— 1.0	— 5.0	Preinsulin (1.4 yr.); no undernutrition; poor control of diabetes; iritis; retinitis proliferans; pyorrhea; late onset of development (16 yr.); at 20 yr. complete development	.....	Long after growth; death from coronary occlusion
	Onset of retardation	16.0						
	Maximal retardation	19.0		— 5.8				
	Last observation	28.8		— 2.5	—10.0			
45	First observation	3.2	1.6	— 3.5	— 5.0	Preinsulin (0.9 yr.); slight undernutrition, then adequate diet; blood pressure 140/80	.....	.....
	Onset of retardation	12.0						
	Maximal retardation	15.5		— 4.0				
	Last observation	19.2		— 1.0	+11.0			
46	First observation	11.2	0.8	— 2.0	—14.0	Poor control; undeveloped at 16 yr.	.....	.....
	Onset of retardation	14.0						
	Maximal retardation	15.5		— 5.3				
	Last observation	26.0		— 4.0	— 4.0			
47	First observation	12.0	1.0	— 2.0	— 2.0	Occasionally hyaline casts	.....	Long after-growth
	Onset of retardation	14.0						
	Maximal retardation	16.0		— 5.0				
	Last observation	28.8		N	+ 3.0			
48	First observation	9.7	1.4	N	— 2.0	Necrobiosis lipoidica diabeticorum	.....	Long after-growth
	Onset of retardation	17.0						
	Maximal retardation	17.0		— 4.4				
	Last observation	22.5		— 2.5	— 8.0			
49	First observation	12.2	0.0	— 1.0	N	No special peculiarities	.....	Long after-growth
	Onset of retardation	16.0						
	Maximal retardation	18.3		— 5.1				
	Last observation	23.0		— 2.3	—13.0			
50	First observation	9.1	0.0	— 2.0	— 7.0	Very poor control; free diet; arteriosclerosis; delayed development	.....	.....
	Onset of retardation	14.0						
	Maximal retardation	18.0		— 5.4				
	Last observation	23.0		— 2.0	— 5.0			
51	First observation	12.0	4.1	— 3.8	— 4.0	Pyorrhea; blood pressure 140/90; retinitis proliferans; undescended testes; at 20 yr. completely developed	.....	.....
	Onset of retardation	14.0						
	Maximal retardation	14.5		— 5.5				
	Last observation	24.1		— 2.0	— 9.0			
52	First observation	5.2	2.0	N	— 3.0	No complications	.....	Good potential of growth
	Onset of retardation	9.0						
	Maximal retardation	12.0		— 6.1				
	Last observation	15.9		— 4.5	— 6.0			
53	First observation	9.2	1.9	— 3.5	— 3.0	Probably potentially diabetic; borderline case; no complications	.....	.....
	Onset of retardation	11.0						
	Maximal retardation	12.5		— 5.0				
	Last observation	19.6		— 1.0	— 8.0			

54	First observation	6.2	4.5	— 5.0	— 1.0	Normal sexual development; rheumatic fever	.....	.....
	Onset of retardation	....						
	Maximal retardation	7.3		— 5.8				
	Last observation	17.9		— 1.0	+ 2.0			
55	First observation	14.9	1.5	— 4.0	—15.0	Borderline case with little retardation; renal stones with hematuria; question of encephalitis; complete development	.....	.....
	Onset of retardation	18.0						
	Maximal retardation	19.0		— 4.5				
	Last observation	25.7		— 4.0	+ 4.0			
56	First observation	13.2	1.8	— 1.0	+13.0	Question of Friedreich's ataxia; at 14 yr. no pubic hair; at 16 yr. axillary hair; at 20 yr. more mature appearance, voice deeper; cataracts; congenital amblyopia with nystagmus	.....	.....
	Onset of retardation	16.0						
	Maximal retardation	17.0		— 4.4				
	Last observation	21.0		— 3.0	— 1.0			
57	First observation	22.7	17.1	— 5.0	N	Preinsulin (6.4 yr.); little growth during period of extreme undernutrition; hair lost and teeth became loose; arteriosclerosis; retinitis; retinal hemorrhages; nearly total blindness and 70 per cent deafness; peculiar lesion of brain and eyes (Leber's dysoptic atrophy)	.....	Only short observation
	Onset of retardation	....						
	Maximal retardation	22.7		— 5.0				
	Last observation	23.7		— 3.5	—10.0			
58	First observation	10.8	4.5	— 4.8	+ 3.0	Hepatomegaly treated with betaine; at 15 yr. completely developed	.....	.....
	Onset of retardation	....						
	Maximal retardation	10.8		— 4.8				
	Last observation	14.7		+ 1.8	+12.0			
59	First observation	6.8	0.0	— 5.3	— 3.0	.....	.....	Good potential of growth
	Onset of retardation	....						
	Maximal retardation	6.8		— 5.3				
	Last observation	10.9		— 4.5	+ 7.0			
60	First observation	7.9	1.7	— 0.5	N	Hepatomegaly; at 14 yr. no pubic or axillary hair	Thyroid	Good potential of growth
	Onset of retardation	10.0						
	Maximal retardation	14.0		— 4.8				
	Last observation	16.2		— 2.5	— 8.0			
61	First observation	11.6	1.4	— 4.3	+ 5.0	At 12 yr. no development; testes very small	Thyroid	.....
	Onset of retardation	....						
	Maximal retardation	14.3		— 6.3				
	Last observation	14.3		— 6.3	+ 6.0			
62	First observation	5.1	0.1	N	— 4.0	Hepatomegaly; neuritis; pyorrhea; repeated attacks of coma; at 14 yr. undeveloped; at 15 yr. pubic hair beginning to appear	Anterior pituitary extract and thyroid	Good potential of growth
	Onset of retardation	9.5						
	Maximal retardation	14.5		— 4.6				
	Last observation	17.2		— 2.0	—10.0			
63	First observation	17.1	7.9	— 3.0	—14.0	Liver enlarged; completely developed at 17 yr.	Anterior pituitary extract (a few injections) and thyroid	Death from sodium pentobarbital (soluble pentobarbital U. S. P.) poisoning
	Onset of retardation	....						
	Maximal retardation	20.7		— 3.5				
	Last observation	20.7		— 3.5	+ 9.0			
64	First observation	5.9	0.0	— 0.5	— 5.0	Large liver; sexual development delayed	Anterior pituitary extract (15 days)	.....
	Onset of retardation	11.0						
	Maximal retardation	13.0		— 5.4				
	Last observation	15.5		— 4.5	+ 7.0			
65	First observation	10.2	1.2	— 0.5	+ 8.0	Father very tall; mother perhaps hypothyroid; at 15 yr. voice changing	Anterior pituitary extract	.....
	Onset of retardation	13.0						
	Maximal retardation	13.8		— 4.6				
	Last observation	17.5		— 2.5	N			

TABLE 18.—*Data on Retarded Diabetic Boys—Continued*

Serial No.		Age, Years	Duration, Years	Deviation of: Height, Inches	Deviation of: Weight, Pounds	Clinical Peculiarities	Therapy for Retardation	Progress
	TRANSITORY INFANTILISM (BOYS)—Continued							
66	First observation	11.5	0.1	— 4.5	+ 5.0	Cryptochidism treated with chorionic gonadotropin; at 15 yr. not developed	Anterior pituitary extract (short time)	.....
	Onset of retardation	15.0						
	Maximal retardation	15.5		— 3.5				
	Last observation	18.0		— 0.5	— 9.5			
	CONSTITUTIONAL (BOYS)							
67	First observation	8.9	0.1	+ 2.0	— 5.0	Nearly blind; cataract and retinitis; empyema	.....	.....
	Onset of retardation	13.0						
	Maximal retardation	17.0		— 6.3				
	Last observation	22.3		— 5.0	+11.0			
68	First observation	11.9	1.8	— 2.0	— 5.0	Casts in urine; retinitis	.....	.....
	Onset of retardation	15.0						
	Maximal retardation	17.0		— 7.4				
	Last observation	26.0		— 5.0	—10.0			
69	First observation	13.9	0.9	— 1.8	— 5.0	Twin of patient 68; retinitis; retinal hemorrhages; iritis; arteriosclerosis; late development at 17 yr.	.....	.....
	Onset of retardation	15.0						
	Maximal retardation	19.0		— 6.8				
	Last observation	25.4		— 6.8	—10.0			
70	First observation	13.8	0.2	— 3.5	+ 1.0	Diabetes poorly controlled; acidosis and carbuncles; at 18 yr. beginning development; voice changing; features childish; at 20 yr. development normal; pubic hair and body hair	.....	Death in coma
	Onset of retardation	15.0						
	Maximal retardation	20.5		— 8.5				
	Last observation	20.5		— 8.5	+ 5.0			
71	First observation	12.9	0.1	— 3.0	+ 3.0	Borderline case; iritis; pyorrhea; sexual development normal	.....	.....
	Onset of retardation	14.0						
	Maximal retardation	22.0		— 5.0				
	Last observation	22.0		— 5.0	— 7.0			
72	First observation	18.3	6.9	— 4.8	—14.0	At 14 yr. developed	.....	.....
	Onset of retardation	....						
	Maximal retardation	20.0		— 5.0				
	Last observation	23.4		— 5.0	—12.0			
73	First observation	10.6	4.3	— 4.5	N	Infantile appearance	.....	Short observation
	Onset of retardation	....						
	Maximal retardation	11.0		— 6.0				
	Last observation	12.6		— 5.0	+ 2.0			
	UNDERNUTRITION (BOYS)							
74	First observation	10.6	0.1	— 1.0	+ 4.0	Preinsulin (5.3 yr.); undernutrition; hepatomegaly	.....	Death in coma
	Onset of retardation	14.0						
	Maximal retardation	16.0		— 6.4				
	Last observation	16.0		— 6.4	—20.0			
75	First observation	16.8	4.1	— 6.1	—27.0	Preinsulin (4.7 yr.); undernutrition; Fröhlich-like syndrome; at 19 yr. little sexual development	.....	Death in coma
	Onset of retardation	....						
	Maximal retardation	19.0		— 7.2				
	Last observation	19.0		— 7.2	—20.0			

nutrition, eventually leads to retardation of growth depending on the duration and the degree of the undernutrition period; the latter, decompensated diabetes, does not necessarily lead to retardation but, being associated with various complications, can involve the entire organism and thus stop growth. So the disturbance of the carbohydrate metabolism is the remote cause of the retardation, perhaps like the blocked absorption of foodstuffs in celiac disease. Still another factor may exist, however, that is, an underlying predisposition to retardation coordinated with the diabetic anlage. Is it only children with this predisposition who may become retarded when exposed to the damage of chronic undernutrition and the various complications of diabetes? It is difficult to decide whether such a predisposition exists, but we know that a great many diabetic children living continuously on the verge of coma grow and develop perfectly. Here again much depends on the period of childhood in which the patient is exposed to the damage of exogenous and endogenous undernutrition. It must not be forgotten that even if there is fairly good control by insulin as far as blood sugar and acidosis are concerned, it is always only a crude attempt compared with the natural and continuous secretory function of the islands.

The clinical picture of the highest degree of retardation in diabetic children will be described later. We shall refer to this condition as "hypopituitary-like dwarfism" or as "diabetic dwarfism" because of its simplicity, though quite unprejudiced by the term.

Classification and subdivision are made on the basis of the clinical peculiarities of the individual patient's cases (tables 17 and 18). From the superimposed complexities of retardation a definite syndrome of diabetic pseudodwarfism can be constructed.

The subdivisions of retardation in our patients (118) according to etiologic factors are as follows: (1) hypopituitary-like, 55.0 per cent (65 patients); (2) transitory infantilism, 27.1 per cent (32 patients); (3) constitutional type, 11.9 per cent (14 patients); (4) undernutrition, 2.5 per cent (3 patients); (5) congenital anomalies, 1.7 per cent (2 patients); (6) neglect, 0.9 per cent (1 patient), and (7) tertiary syphilis, 0.9 per cent (1 patient).

The hypopituitary-like dwarfs and children with transitory infantilism furnish the main contingents in the total group. Differential diagnosis between hypopituitary-like and constitutional types and transitory infantilism is sometimes difficult or impossible, as is also differentiation between these three types and undernutrition and neglect. Hypopituitary-like dwarfism is the most important type among the retarded diabetic children.

If one constructs in the manner of Galton's biometric technic an average ideal diabetic dwarf having the prominent features of the majority of the children involved, one would obtain the following picture: (1) a history of diabetes of long standing but not usually over

6 years; (2) a retardation in height of 10 to 20 and infrequently over 20 per cent; (3) a tendency to plus variations of body weight or actual obesity; (4) infantile proportions when the onset is early; (5) markedly delayed osseous differentiation and late fusion of the epiphyses; (6) delay in appearance or complete absence of extragenital sex characteristics (often in boys a feminine type of fat deposit and small testes and in girls amenorrhea); (7) normal mental development; (8) infantile psyche; (9) a good prognosis when treatment is given early and adequately with thyroid and with anterior pituitary extract containing the growth hormone (discussed in section IV); (10) external similarity to hypopituitarism and glycogen storage disease; (11) hepatomegaly in many cases; (12) low insulin requirement at the onset, higher during

TABLE 19.—*Time of Onset of Diabetes, Retardation and Maximum Retardation and Maximal Minus Deviation in Inches in Diabetic Dwarfism*

	Hypopituitary-like		Transitory Infantilism		Constitutional	
	Average	Mean	Average	Mean	Average	Mean
Age at onset of diabetes						
Boys	7.1	6.4	8.1	8.7	10.9	11.4
Girls	5.1	5.4	4.1	3.1	10.1	9.3
Average for both sexes	6.4		7.1		10.5	
Age at onset of retardation						
Boys	10.5	10.0	13.7	14.0	15.1	15.0
Girls	9.6	10.0	8.7	9.0	10.8	10.8*
Average for both sexes	10.2		12.4		14.0	
Age at maximum retardation						
Boys	15.8	16.0	15.5	15.5	17.8	19.0
Girls	14.4	14.5	12.8	13.0	14.2	14.0
Average for both sexes	15.4		14.7		16.3	
Average maximal minus deviation in inches						
Boys	8.8	8.5	4.9	5.0	6.4	6.3
Girls	8.9	8.7	6.5	6.3	7.1	6.6
Average for both sexes	8.8		5.3		6.7	

* Two subjects.

and after treatment with anterior pituitary extract; (13) occasionally other congenital anomalies and abnormal response to exogenous factors; (14) usually an increase in the basal metabolic rate, with the specific dynamic action normal; (15) no geroderma; (16) tendency toward complications of diabetes (cataracts, arteriosclerosis, etc.). The true incidence of this special form of diabetic pseudodwarfism is 4.6 per cent of our entire group of 1,407 children; that is, every twenty-second diabetic child is a potential hypopituitary-like dwarf.

Transitory infantilism is the next type in order of frequency (27.1 per cent). This anomaly is well known to the pediatrician and occurs more frequently in boys. There was an incidence of 32.0 per cent among the retarded boys and of 18.6 per cent among the retarded girls. Characteristic were a good potential of growth and spontaneity of the repair of failure of both height and sexual development. Some of the children eventually reached the expected height. The incidence of transitory

infantilism among all our diabetic children is 2.3 per cent, which means that every forty-fifth diabetic child is a potential victim of infantilism.

The constitutional type has one characteristic peculiarity—a smaller physique. The growth curve runs parallel with the expectation curve. The differentiation is fairly good. There is no response to therapy. The patients become definitely retarded (minus 4 inches) comparatively late

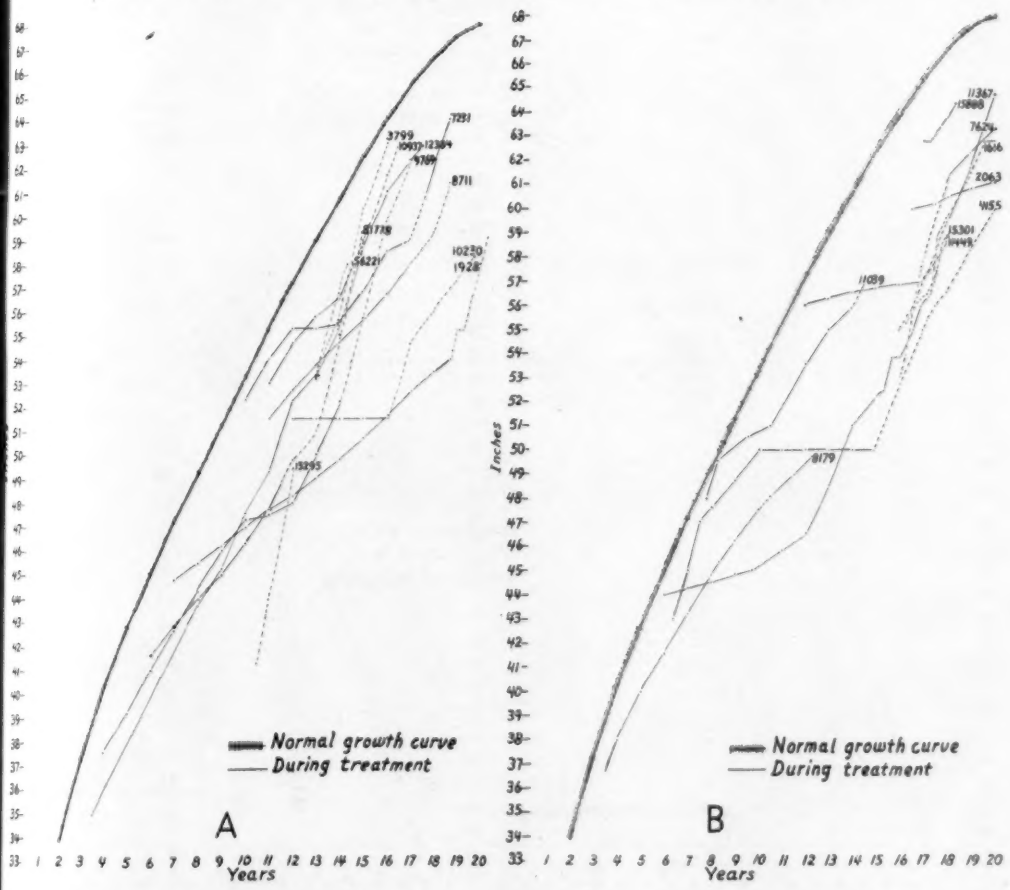

Chart 8.—Growth curves (*A*) of 11 retarded diabetic boys (mixed group) treated with anterior pituitary extract and (*B*) of 10 retarded diabetic boys (mixed group) treated with thyroid.

and usually at the time of pubescence. The pubertal spurt of growth is less pronounced, so that the retardation is more manifest at that time. They do not show a long after-growth but remain permanently under the expected height.

The onset of diabetes is earlier among the male hypopituitary-like dwarfs than among the boys with the other two major forms of dwarfism (table 19). Retardation was noted earlier after the onset of diabetes

and was progressive over a longer period of time to attain a higher maximum. Among the girls also the hypopituitary-like group attained a higher maximal minus deviation more slowly than the other two groups, but the time of onset of retardation did not precede that of the other two groups as was seen among the boys. The differences in degree of retardation and in the duration of the period of progressive retardation

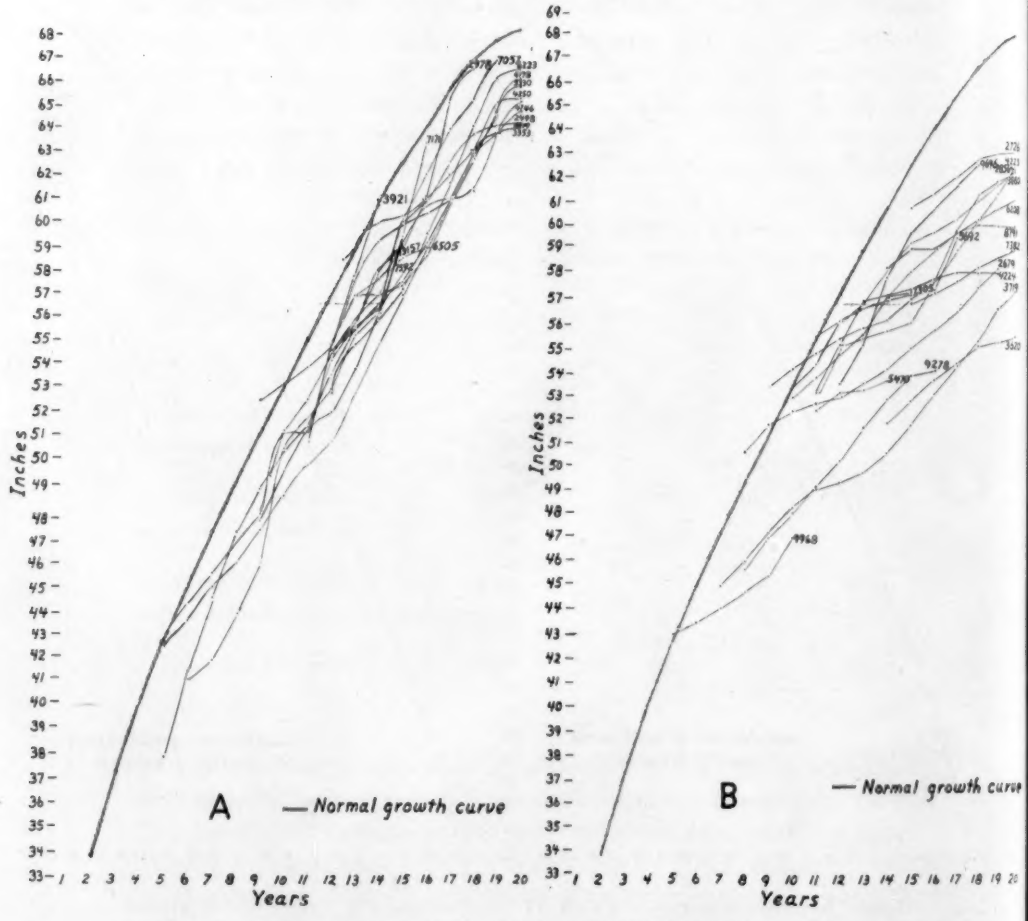

Chart 9.—Growth curves (*A*) of 15 retarded diabetic boys with transitory infantilism and (*B*) of 17 untreated retarded diabetic boys (mixed group).

are confirmatory evidence of the justification of our previous separation of these stunted children into these three major groups.

Neglect is considered the underlying cause of retardation in a diabetic child if one can prove that growth is reestablished by adequate treatment of diabetes alone. This is often difficult, since the children are known to be habitual diet breakers; therefore, such treatment must be carried out over a long period under supervision in a hospital or camp. Clinically

these children have all the signs of uncontrolled diabetes, such as a large output of sugar, a high blood sugar level, frequent positive acetone reactions, high cholesterol values, severe pyorrhea with loosening of the teeth and infections of the skin. Many patients never become retarded in spite

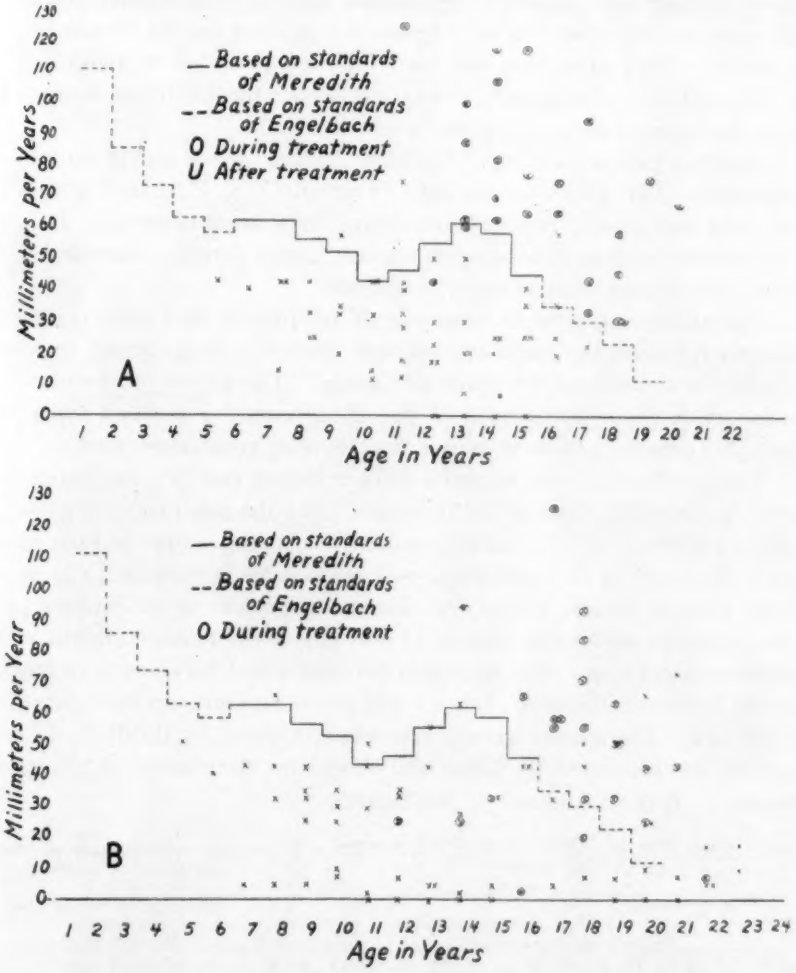

Chart 10.—Velocity of growth (*A*) of 12 retarded diabetic boys treated with anterior pituitary extract and (*B*) of 11 retarded diabetic boys treated with thyroid.

of constant decompensation. Perhaps only those predisposed to retardation will eventually respond in this manner to the exogenous damage of neglect.

IV. TREATMENT

All the patients are divided into three groups in order to observe the response to therapy: (1) patients treated with anterior pituitary

extract containing the growth hormone and with thyroid; (2) patients treated with thyroid alone, and (3) untreated patients. All three groups include patients with more than one type of retardation. The children with transitory infantilism are analyzed separately. It is always possible that a patient with transitory infantilism may be treated with anterior pituitary extract or with thyroid before it is evident that he should be so classified. This procedure has been followed in order to avoid delay in the treatment of retardation, since the sooner the treatment is started after the onset of retardation, the better the result.

Anterior pituitary extract (Squibb or Parke, Davis) was given intramuscularly, 3 cc. every second day. Thyroid U. S. P., 1 to 3 grains a day, was also given. Signs of overdosage were never observed. It is a well known fact that children with normal thyroid function tolerate large doses of the drug without any disturbance.

Successful results in the treatment of retardation have been reported recently following the use of testosterone. A few of the retarded diabetic children have received this form of therapy. The period of observation is too short for a comparison of the effectiveness of the two types of therapy (anterior pituitary extract and thyroid, and testosterone).

Three different types of charts were drawn of each sex separately in order to study the effect of the treatment: (1) the usual form of growth charts (charts 8 and 9), called cumulative charts because at each new point the length of the preceding observation is again included; (2) spot maps (charts 10 and 11) of the velocity of growth in millimeters per year, and (3) spot maps (charts 12 and 13) of the relative growth rate in per cent per year. The standards between 6 and 16 years were based on the figures of Meredith; below 6 and above 16 years, on the figures of Engelbach. The relative growth rate was introduced by Brody.[31] (This method was also used by Bayer and Gray[32] in their study of pituitary dwarfs.) It is represented by the formula:

$$\frac{\text{Height at end of period} - \text{height at beginning of period}}{\text{Average height}} \times \text{Period as decimal part of year}$$

For instance:

Stature at beginning..... 99 cm.
Stature at end.....101 cm.
Period[33] ..... 3 months

$$\text{Relative growth rate} = \frac{101 - 99}{100} \times \frac{1}{0.25} = \frac{2}{25} = 8 \text{ per cent}$$

31. Brody, S.: Growth and Development: III. Growth Rates; Their Evaluation and Significance, Research Bulletin 97, University of Missouri, College of Agriculture, Agricultural Experiment Station, January 1922.

32. Bayer, L. M., and Gray, H.: Pituitary Dwarfs: Their Growth and Treatment; Observations on Twelve Cases for Periods of One to Eight Years, California & West. Med. **47**:228-233 (Oct.) 1937.

33. In our analysis the time period was always one year.

Individual charts of each case were not made, since the whole group was taken as one unit. Only the boys' charts are included in this paper. We have plotted the velocity and the relative growth rate for the entire year even if the patient was not treated throughout the year. This is permissible if the standards with which the values are compared are

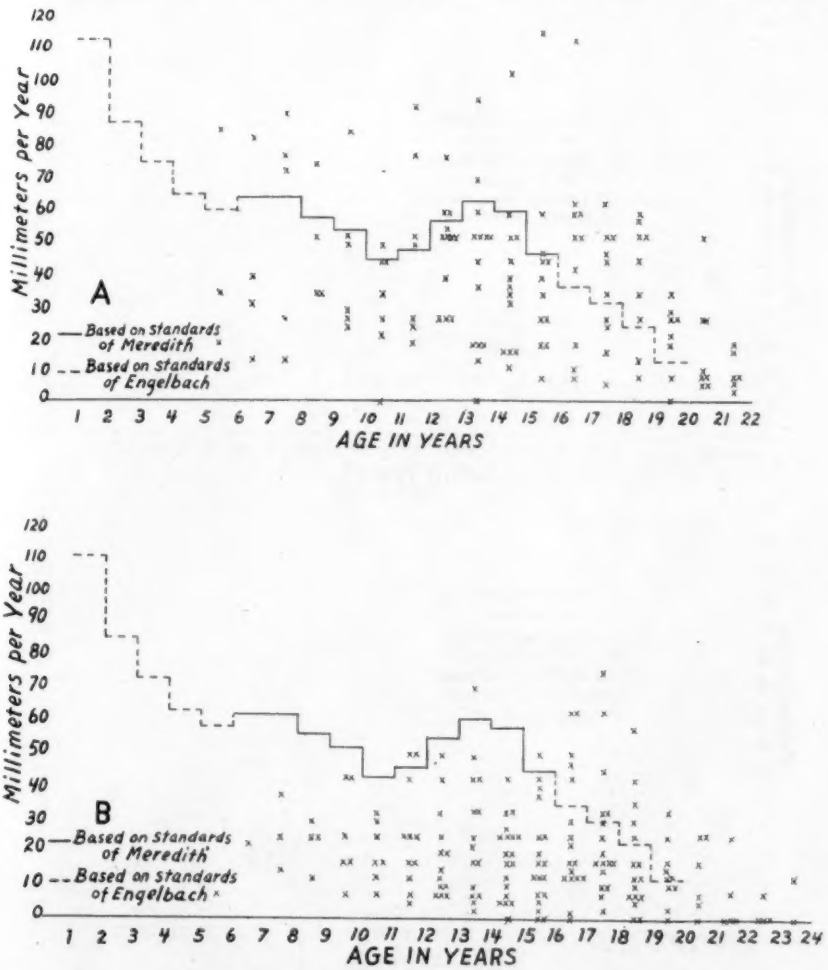

Chart 11.—Velocity of growth (*A*) of 16 retarded diabetic boys with transient infantilism and (*B*) of 26 untreated retarded diabetic boys.

also based on one year periods. Even if a patient is treated for only a few months the growth rate in the subsequent months may be altered by the preceding treatment; so it is more accurate to take this longer period to decide whether velocity and relative growth rates are increased.

Anterior pituitary extract combined with thyroid exerts a very definite stimulating effect on the growth in diabetic pseudodwarfism. The results for the boys can be easily read from the charts. The same results were seen in the girls. Values several points above the expectation in the group of untreated subjects' cases are probably due to the

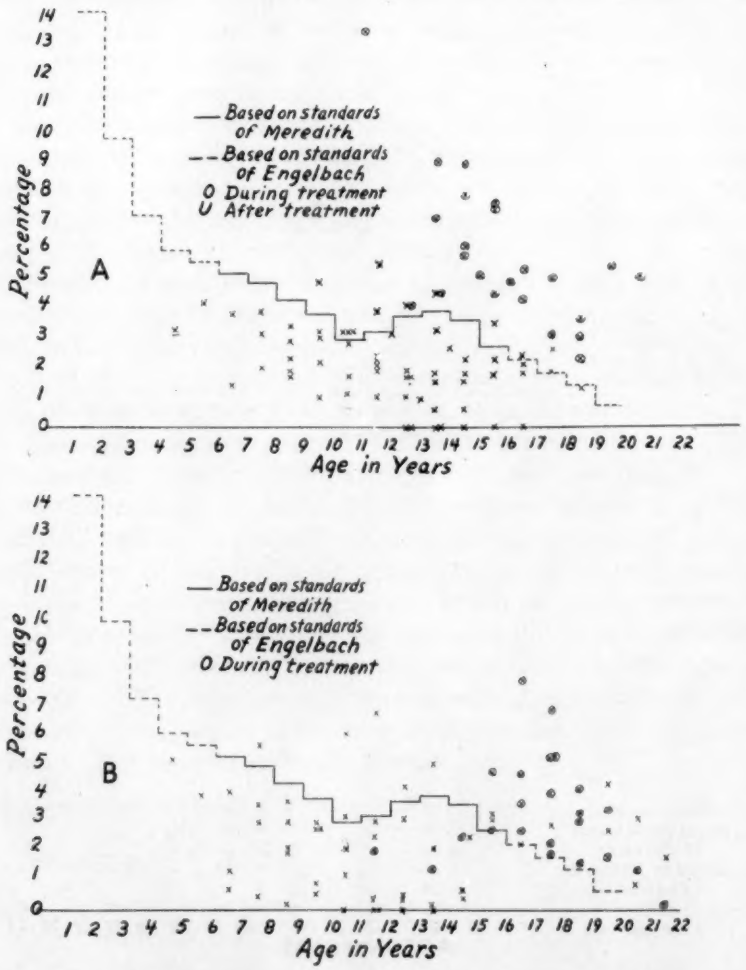

Chart 12.—Relative rate of growth (*A*) of 12 retarded diabetic boys treated with anterior pituitary extract and (*B*) of 11 retarded diabetic boys treated with thyroid.

fact that some children with transitory infantilism were included. The question arises: Is the administration of anterior pituitary extract a true substitutional therapy, like administration of thyroid to cretins, or does it merely exert a stimulating action on growth, controlled by the anterior

lobe of the pituitary gland? Experiments on normal animals seem to make the latter explanation probable. Sexual development and good differentiation paralleled progress in growth.

Thyroid also increases the velocity of growth. A few failures occurred, as may be seen, for instance, in chart 12 *B*; therefore, we would

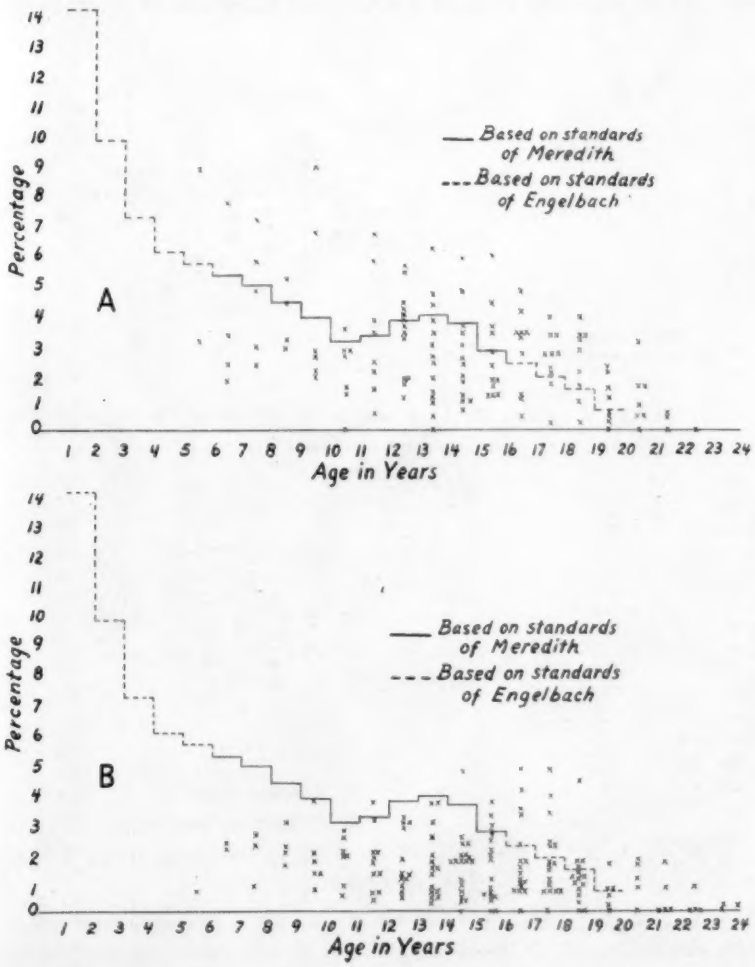

Chart 13.—Relative rate of growth (*A*) of 16 retarded diabetic boys with transient infantilism and (*B*) of 26 untreated retarded diabetic boys.

recommend that thyroid should be used in combination with anterior pituitary extract. If one accepts the theory that thyroid increases the velocity of growth by action on the eosinophilic cells of the anterior lobe of the pituitary, one readily understands that direct treatment with anterior pituitary extract must be more efficacious.

Growth is possible long after one would expect it, as may be seen in the charts. It must be emphasized again that early treatment gives the best results and that treatment should be continued as long as the epiphyses are open.

Endocrine treatment increased the insulin requirement of these patients. The quotients units of insulin over kilograms of body weight

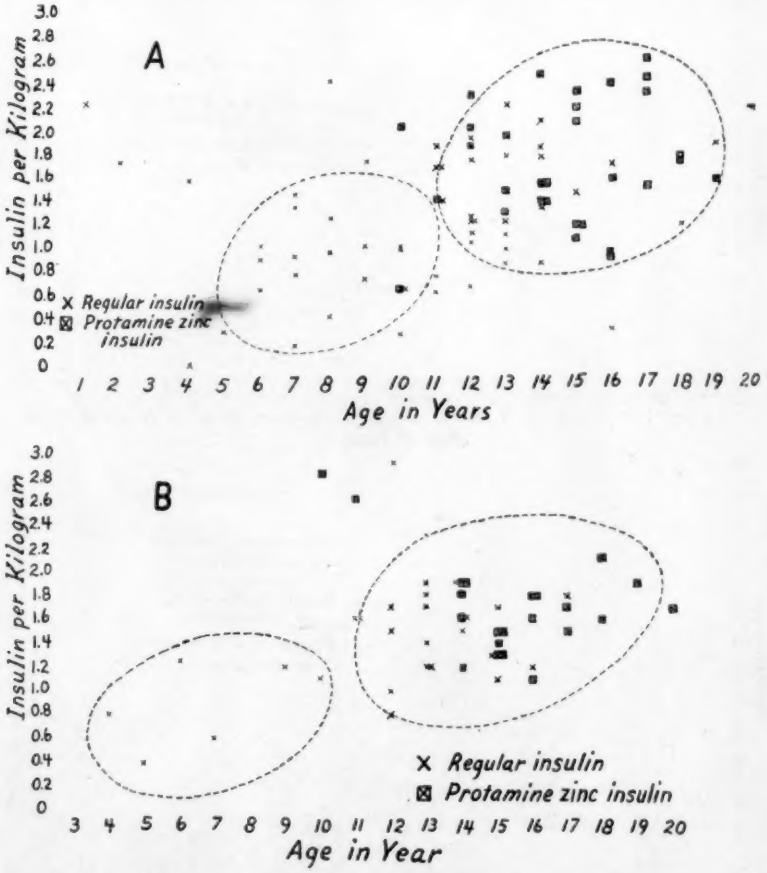

Chart 14.—Insulin requirement (*A*) of 15 retarded boys treated with anterior pituitary extract and (*B*) of 9 retarded girls treated with anterior pituitary extract.

of the retarded children in different age periods are shown in charts 14 to 16. The quotients for 15 retarded boys and 9 retarded girls treated by methods discussed later are shown in chart 14; for 26 untreated retarded boys, in chart 15 *A*, and for 25 nonretarded boys and 25 nonretarded girls with diabetes of approximately ten years' duration, in chart 15 *B* and *C*. The quotients of a special control group of 25 tall diabetic children are shown in chart 16 *A*. These charts show that the highest

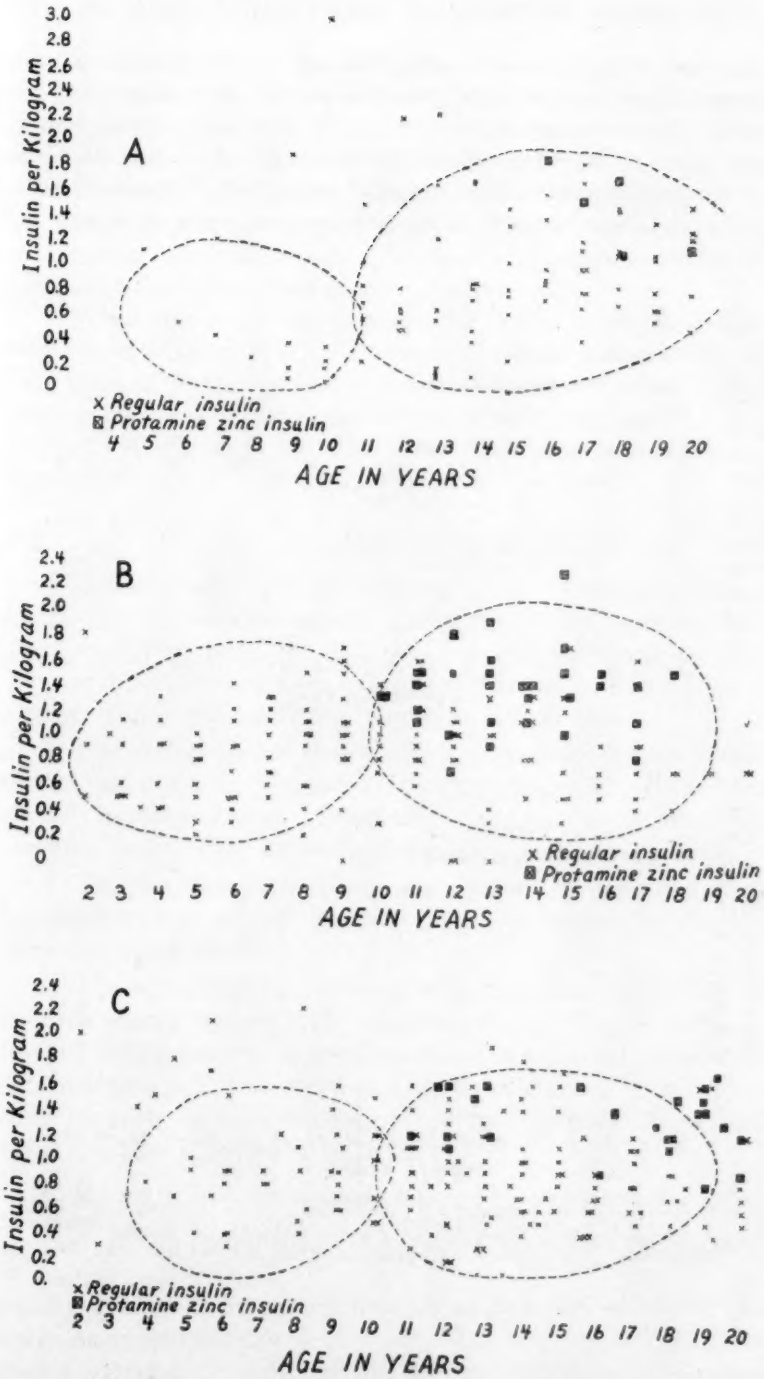

Chart 15.—Insulin requirement (*A*) of 26 untreated retarded diabetic boys, (*B*) of 25 nonretarded boys with diabetes of ten years' duration and (*C*) of 25 nonretarded girls with diabetes of ten years' duration.

insulin–body weight quotients were observed in the group of retarded children treated with anterior pituitary extract from their tenth year onward. In this age period most of the children were treated with this extract alone. Untreated retarded children (20 boys, chart 15 *A*) and 50 nonretarded children (25 boys and 25 girls, chart 15 *B* and *C*) served as controls. Their quotients in the corresponding age groups were defi-

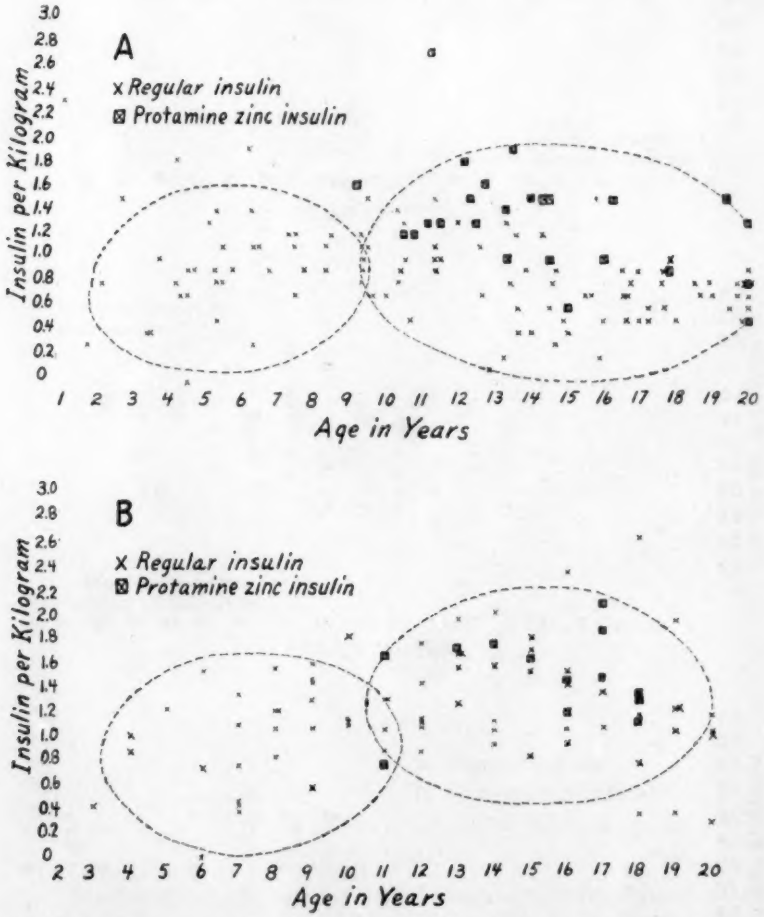

Chart 16.—Insulin requirement (*A*) of 25 tall diabetic children and (*B*) of 17 retarded diabetic children (13 boys and 4 girls) treated with thyroid.

nitely below the quotients in the two groups given anterior pituitary extract. It is known that individual diabetic patients require an increasing amount of insulin with growth and development; therefore, a special control group of 25 very tall diabetic children and juveniles (height

ranging from plus 2 to plus 11 inches [5 to 28 cm.]) were selected. Their quotients (chart 16 *A*) corresponded to those of the untreated subjects and the patients with diabetes of ten years' duration and were definitely below the quotients of the patients treated with anterior pituitary extract. The groups given the anterior pituitary extract showed an insulin requirement greater than that based on body weight and development, a fact which was to be expected, since the pituitary extract exerts a diabetogenic effect in normal animals.

Thyroid treatment, too, increases the insulin requirement based on body weight (chart 16 *B*). The quotients were also definitely higher than those of the control groups (chart 15 *B* and *C*), even if the results were a little less striking than in the group given anterior pituitary extract. It is known that thyroid exerts a stimulating effect on the eosinophilic cells of the anterior lobe of the pituitary.

GENERAL SUMMARY AND CONCLUSIONS

1. A classification of the retarded group according to causation resulted in the following figures: hypopituitary-like dwarfism, 55.0 per cent; transitory infantilism, 27.1 per cent; constitutional type, 11.9 per cent; undernutrition, 2.5 per cent; congenital anomalies, 1.7 per cent; neglect, 0.9 per cent, and tertiary syphilis, 0.9 per cent.

2. The clinical picture of hypopituitary-like diabetic pseudodwarfism is described in detail. The average incidence among all juvenile diabetic patients is 4.6 per cent. Obligatory symptoms are stunted stature, abnormal proportions, delayed differentiation and hypogenitalism.

3. The best therapeutic results are obtained by early and thorough treatment with an anterior pituitary extract containing the growth hormone and with thyroid.

4. The highest insulin over body weight quotients were found in the children treated with anterior pituitary extract. The quotients in the thyroid-treated group were also elevated. The untreated patients showed approximately the same range as a group of children with diabetes of about ten years' duration and a special group of very tall diabetic children (plus 2 to plus 11 inches [5 to 28 cm.]).

Dr. Howard V. Meredith permitted us to use his standards before publication, Dr. Harold C. Stuart permitted us to study the records of a group of children under his care and Dr. Eli Friedman gave us the opportunity to examine a group of underprivileged children.

AMYLASE–ACCELERATING ACTION OF GASTRIC CONTENTS

WILBURT C. DAVISON, M.D.
DURHAM, N. C.

The gastric contents of infants usually contain a certain amount of amylase as a result of the presence of swallowed saliva [1] and regurgitated duodenal juice, but, even excluding this amount, the addition of gastric contents to pancreatic extract (fresh hog pancreas extracted in saline solution) increased its starch-liquefying activity nearly eightfold (table). As duodenal contents rarely can be collected without some contamination

Amylase-Accelerating Action of Gastric Contents

Mixture	Units of Amylase per Cc. of Mixture (Viscometric Method) *
Gastric contents alone	1,280
Pancreatic extract alone	40,000
Pancreatic extract and gastric contents	316,000

* Davison, W. C.: A Viscometric Method for the Quantitative Determination of Amylase, Bull. Johns Hopkins Hosp. **37**: 281-282 (Oct.) 1925.

with gastric contents, the results of the determination of the amylase values of duodenal contents will vary with the degree of admixture of gastric contents.[2]

From the departments of pediatrics of the schools of medicine of Johns Hopkins University and Duke University.

1. Davison, W. C.: Gastric Analyses in Normal Infants and Those Convalescent from Diarrhea, Am. J. Dis. Child. **30**:23-32 (July) 1925.

2. Davison, W. C.: The Duodenal Contents of Infants in Health and During and Following Diarrhea, Am. J. Dis. Child. **29**:743-756 (June) 1925. Kajdi, L., and Davison, W. C.: Chemical and Enzymic Studies of the Duodenal Contents of Infants, to be published. Davison, W. C.: Difficulties in the Enzymic Titration of Duodenal Contents, to be published.

QUANTITATIVE AND QUALITATIVE PLATELET VALUES OF NORMAL NEWBORN INFANTS

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In 1936 Leslie and one of us [1] reported the quantitative and qualitative platelet values in the blood of 40 normal newborn infants. Since this time we have shortened and simplified the method used until we now believe that it may be easily and simply employed in any laboratory. As one of the principal changes from our original method is the shortening of the plasma centrifugation, which will conversely reduce the coagulation time of the plasma fractions, the following study was made.

PROCEDURE

The method of qualitative and quantitative platelet analysis was used as formerly described.[2] Blood was withdrawn directly from a vein in chilled oiled syringes, and any sample containing cerebrospinal or tissue fluid was discarded.

It must be emphasized that if any difficulty is encountered in obtaining the blood so that there is addition of tissue fluid or cerebrospinal fluid, the results will be unreliable. This can be immediately detected by the platelet count. It will be lower than anticipated, and the platelets will show clumping and variation in size. Any platelet count of less than 100,000 should be viewed with suspicion and the determination repeated. If the procedure is carried out under these conditions, one of two things will occur: First, all coagulation times will be abnormally short, or plasma B may even coagulate in the centrifuge tube. This should be suspected if plasma A coagulates in less than four minutes. Secondly, in the opposite extreme, all coagulation times may be abnormally long and plasma B may never coagulate because coagulation has occurred and the supernatant fluid is serum rather than plasma.

Blood was withdrawn from the cord immediately after birth and from the infant daily thereafter. The determinations were made on the same baby for consecutive

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From the Department of Pediatrics, Rush Medical College, and the Presbyterian Hospital.

Funds for this study were obtained by a grant from the Elizabeth McCormick Fund of the Institute of Medicine, Chicago.

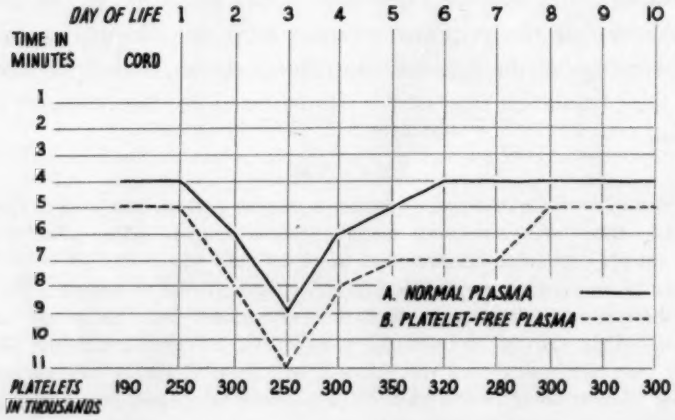
1. Sanford, H. N., and Leslie, E. I.: The Substance Involved in the Coagulation of the Blood of the Newborn, Am. J. Dis. Child. **51**:590 (March) 1936.

2. Sanford, H. N., and Leslie, E. I.: An Improved Method for the Estimation of Quantitative and Qualitative Platelet Factors, J. Lab. & Clin. Med. **27**:255 (Nov.) 1941.

days, and no baby is included in this study for whom daily determinations were not made for at least five days after birth.

Platelet counts were made directly from natural venous plasma obtained after centrifugation of whole blood in chilled 1 cc. tubes coated with a mixture of paraffin and liquid petrolatum for one and one-half minutes at 5,000 revolutions per minute. Qualitative determinations of the platelets were made by estimating the coagulation time of the natural plasma, called plasma A, and of the platelet-free plasma, obtained by centrifugation for fifteen minutes, called plasma B.

The study consisted of 356 quantitative and qualitative platelet estimations on 55 individual newborn infants. Thirty-four of these infants were entirely breast fed, receiving nothing except what they could obtain from the breast and sterile water during the newborn period. Twenty-one were partially breast fed, receiving a complement of equal parts of milk and water with 5 per cent cane sugar immediately after birth and thereafter as was necessary for adequate nutrition. As this



Qualitative platelet factors as shown in 356 determinations on 55 individual newborn infants.

study was carried on over a period of two years, seasonal periods were noted as well as type of delivery and general condition of the infant.

RESULTS

The results are shown graphically in the chart.

COMMENT

This method shows platelet counts of the blood of normal adults to vary between 100,000 and 400,000 per cubic millimeter. The coagulation time for their natural plasma (plasma A) is between four and eight minutes and for the platelet-free plasma (plasma B) between six and ten minutes. It will be observed that quantitatively the platelet counts of the newborn are not different from adult values, but that qualitatively

there is a decrease in coagulation activity in newborn infants' platelets, which increases the coagulation time of the plasma over adult values for the first week of life.

This is in no way due to the gross number of platelets in the plasma of the newborn, which remain uniformly between 250,000 and 350,000 per cubic millimeter, but is the result of a qualitative change. The average coagulation time of the natural venous plasma ir four minutes for cord blood and four minutes on the first day of life. The coagulation time increases rapidly to six minutes on the second day of life and reaches a maximum of nine minutes on the third day of life. It then falls to six minutes on the fourth day and to five minutes on the fifth day. Thereafter it remains at four minutes throughout the newborn period. This corresponds, of course, to the coagulation time of the whole blood, as was described by Rodda.[3]

It has been stated that this increase in the coagulation time of the whole blood in the newborn is due to the reduction of prothrombin in the blood plasma.[4] Whether this diminution of plasma prothrombin is the cause of the increase or lengthening of the coagulation time of the whole blood either wholly or in part is open to considerable discussion. We believe that a qualitative platelet defect which exists in the newborn period plays an important role in the coagulation reaction. This is demonstrated by the platelet-free plasma (plasma B). This is plasma which has been shown by microscopic examination to contain no intact platelets. There has been no change in the prothrombin content of this plasma, yet with the same amount of plasma prothrombin that exists in natural plasma (plasma A) the coagulation time of the platelet-free plasma increases to five minutes for cord blood on the first day of life and eight minutes on the second day of life. It is further increased to eleven minutes on the third day of life. It then decreases to eight minutes on the fourth day of life and to seven minutes during the next three days. From the eighth day of life it falls to five minutes and continues at this value throughout the newborn period. The decrease in the coagulation ability of this plasma must represent only changes in the thromboplastin obtained by the disintegration of the platelets, so that it may be interpreted as a measure of the qualitative value of the platelets.

It is of interest to note that this increased resistance of the platelets to disintegration, a qualitative defect that parallels the increase in coagulation time of the whole blood, is similar to the decrease in pro-

3. Rodda, R. D.: A Clinical Method of Estimating the Coagulation Time of the Blood, Am. J. M. Sc. **140**:807, 1910.

4. Quick, A. J., and Grossman, A. M.: The Nature of Hemorrhagic Disease of the Newborn, Am. J. M. Sc. **199**:1 (Jan.) 1940.

thrombin, fibrinogen [5] and calcium [6] that occurs during this period of life. Yet the coagulation time of the whole blood of the newborn is shorter than that of the adult.

We were unable to find any difference in qualitative or quantitative platelet values in the newborn due to parity of the mother, type of delivery, weight of the baby, type of feeding or seasonal incidence. We could also find no change in these factors associated with the occasional hemorrhages seen in the newborn period. It must be remembered, however, that in no instance of such hemorrhages was the coagulation time of the whole blood increased over five minutes, which we consider to be the criterion of true hemorrhagic disease of the newborn.

CONCLUSIONS

Quantitatively there is no particular change in the platelets of the newborn for the first ten days of life. Qualitatively the platelets of the newborn show increasing resistance to disintegration until the fourth day of life, after which there is a slow return to normal (same as adult) coagulation time by the end of the newborn period.

952 North Michigan Avenue.

5. Crane, M. M., and Sanford, H. N.: Variations of the Fibrinogen Content in the Normal Infant, Am. J. Dis. Child. **51**:99 (Jan.) 1936.

6. Bakwin, H.: Tetany in Newborn Infants, J. Pediat. **14**:1 (Jan.) 1939.

Case Reports

LAURENCE-MOON-BIEDL SYNDROME

ITS OCCURRENCE IN A NEGRO CHILD; TREATMENT WITH GONADOTROPIN AND ANDROGEN

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The so-called Laurence-Moon-Biedl syndrome is a fairly rare [1] condition characterized by six cardinal signs, namely obesity, atypical retinitis pigmentosa, mental deficiency, genital dystrophy, polydactylism and familial occurrence. In the literature a number of associated anomalies have been reported,[2] such as genu valgum, coxa vara, scoliosis, shortness of the hands and feet, dwarfism, deformities of the skull, deafness, strabismus, nystagmus and congenital heart disease. All of the patients whose cases are described under this diagnosis do not present the complete classic syndrome. Thus of 102 patients data on whom were tabulated by Warkany, Frauenberger and Mitchell [1b] only 24 exhibited the complete syndrome. Males apparently are affected more often than females.

Although this condition was first described by Laurence and Moon [3] seventy-five years ago, it remained for Bardet [4] and Biedl [5] to recognize

From the Division of Pediatrics and the Division of Orthopedic Surgery, Howard University College of Medicine and Freedmen's Hospital.

1. (*a*) Cockayne, E. A.; Krestin, D., and Sorsby, A.: Obesity, Hypogenitalism, Mental Retardation, Polydactyly and Retinal Pigmentation: The Laurence-Moon-Biedl Syndrome, Quart. J. Med. **4**:93, 1935. (*b*) Warkany, J.; Frauenberger, G. S., and Mitchell, A. G.: Heredofamilial Deviations, Am. J. Dis. Child. **53**:455 (Feb.) 1937. (*c*) Marmor, J., and Lambert, R. K.: Laurence-Moon-Biedl Syndrome, Arch. Int. Med. **61**:523 (April) 1938. (*d*) Reilly, W. A., and Lisser, H.: Laurence-Moon-Biedl Syndrome, Endocrinology **16**:337, 1932. (*e*) Hecker, A. O., and Warren, V. C.: Girdle Type Adiposity Among Mentally Deficient Males, Am. J. Dis. Child. **54**:1257 (Dec.) 1937.

2. (*a*) Weiss, E.: Cerebral Adiposity with Nerve Deafness, Mental Deficiency and Genital Dystrophy (A Variant of the Laurence-Biedl Syndrome), Am. J. M. Sc. **183**:268, 1932. (*b*) Levingston, A. G.: Laurence-Moon-Biedl Syndrome, Am. J. Dis. Child. **53**:1534 (June) 1937. (*c*) Arena, J. M.: Laurence-Biedl Syndrome, J. Pediat. **10**:62, 1937. (*d*) Cooperstock, M.: Laurence-Moon-Biedl Syndrome, Am. J. Dis. Child. **54**:334 (Aug.) 1937. (*e*) Ellis, R. W. B., and Law, F. W.:

(Footnotes continued on next page)

the symptom complex as constituting a distinct clinical syndrome. The first description in this country was published in 1925 by Solis-Cohen and Weiss.[6] In recent years comprehensive reviews on the subject have been made by Reilly and Lisser,[1d] Cockayne, Krestin and Sorsby [1a] and Warkany, Frauenberger and Mitchell.[1b]

In their 1935 review of the subject Cockayne and his associates [1a] stated that the condition had not yet been reported as occurring in the Negro. Warkany and his co-workers [1b] described an atypical "incomplete" form in a 16 year old Negro boy in 1937. The following case is reported because it is one of the very few instances of the typical syndrome in a Negro to be described. Moreover an effort was made to evaluate the effect of both gonadotropin and androgen (testosterone) on the hypogenitalism exhibited by the patient.

REPORT OF A CASE

W. W., a Negro boy aged 12 years, was brought to the hospital because of deformity of the left leg. There was also a history of obesity, hypogenitalism, mental deficiency, defective vision, polydactylism and impaired hearing.

Family History.—The mother, aged 57 years, was of medium stature and was healthy. She experienced no trouble with her eyes as a child but had worn glasses since the age of 35 years. There had been no miscarriages. The maternal family history revealed no evidence of obesity, polydactylism, mental deficiency or defective vision or hearing. The father, aged 59 years, was healthy and of large stature. He was mildly myopic as a child but did not begin to wear glasses until the age of 45 years. Polydactylism was a definite hereditary feature on the father's side. Several members of the father's family had been afflicted with a maniacal form of insanity. There was no history of consanguinity.

The two eldest siblings were 29 and 26 years old respectively and were college graduates. They were not obese and were described as being of normal build. The third sibling, a 20 year old man, was obese; "glandular extract" had been prescribed in his childhood, at the age of 8 years, without apparent benefit. He had been afflicted with poor vision all of his life. He was mentally dull and exhibited polydactylism (extra toes). His fingers and hands were described as being short. The patient was the product of the mother's fourth and last pregnancy.

Birth and Developmental History.—The patient was prematurely born after seven months' gestation, weighing 3 pounds (1,307 Gm.). Labor was prolonged, and the mother was of the opinion that a forceps was used to effect delivery. At

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Infantilism, Obesity and Retinal Dystrophy: A 'Forme Fruste' of the Laurence-Moon-Biedl Syndrome, Arch. Dis. Childhood **16**:105, 1941.

3. Laurence, J. Z., and Moon, R. C.: Ophth. Rev. **2**:32, 1866.

4. Bardet, G.: Sur un syndrome d'obésité congénitale avec polydactylie et rétinite pigmentaire, Thesis, Paris, no. 470, 1920.

5. Biedl, A.: Deutsche med. Wchnschr. **48**:1630, 1922.

6. Solis-Cohen, S., and Weiss, E.: Dystrophia Adiposogenitalis, with Atypical Retinitis Pigmentosa and Mental Deficiency—the Laurence-Biedl Syndrome, Am. J. M. Sc. **169**:489, 1925.

birth he exhibited six fingers on the right hand and six toes on each foot. He was breast fed. He held his head erect at 6 months, sat without support at 8 months, walked at 15 months and began to talk in sentences at 2 years. He entered school at the age of 5 years, but at 12 years he had advanced only to the fourth grade, where he had remained for the past three years. He had never learned to read or write with any degree of proficiency. His mother attributed poor progress in school to defective vision and poor memory. The patient and his 20 year old brother were definitely developmentally retarded, in contrast to the two normal eldest siblings.

Past Medical History.—The patient's eyesight had been poor since infancy and was extremely defective at night. His hearing always had been impaired. He began to gain rapidly in weight after the age of 2 years. Attacks of measles and pertussis of moderate severity occurred at the age of 3 years. In August 1935 one of us (P. T. J.) amputated the extra digit from each foot and from the right hand. During 1938 and 1939 the mother had observed progressive bowing of the boy's left leg.

There was never any gross disturbance of behavior. The patient was described by the mother as being quiet and good natured with a tendency to sedentary habits. His appetite was excellent, and he was especially fond of carbohydrates. The mother thought that he passed large amounts of urine. There were no convulsions at any time.

Physical Examination.—The patient (fig. 1) was a quiet, phlegmatic, obese boy whose head appeared small for his large body. The speech was dysarthric and indistinct. Hearing and vision were obviously defective. He was cooperative and carried out simple requests as asked. The temperature and respiration were normal. The pulse rate was 80 per minute. The systolic blood pressure was 105 and the diastolic 65. The skin was smooth and of fine texture. Leukodermic spots intermingled with hyperpigmented areas gave the skin a mosaic pattern in some places, particularly on the penis and the extremities.

The obesity was of moderate grade and was of the Fröhlich type. The fat was distributed mainly in the mammary, suprapubic and girdle regions. The head was somewhat flattened over the occiput. The tympanic membranes were of normal appearance. The pupils reacted normally to light and in accommodation. Bilateral rotary nystagmus was present, and the right eye exhibited a constant divergent strabismus. The optic disks were pale and vertically oval. The retinal arteries were thin. A small deposit of pigment was observed in the periphery of the right fungus. The consulting ophthalmologist diagnosed atrophy of the optic nerve, myopia, astigmatism, concomitant divergent strabismus and chorioretinal degeneration (atypical retinitis pigmentosa).

The premaxilla protruded, whereas the mandible was small and recessive (micrognathia), causing marked dental malocclusion. The lower central incisors were small, crowded and poorly alined. The hard palate was V shaped and high arched. The tonsils were enlarged. The neck was short and thick. The thyroid gland was normal to palpation. The lungs and heart were normal. The abdomen was normal except for an apron of fat in the suprapubic area.

On the patient's admission (fig. 2) the external genitals were poorly developed and pubic hair was quite sparse. The penis and scrotum were unusually small, even when the surrounding fat was retracted. The testes could not be palpated under any circumstances.

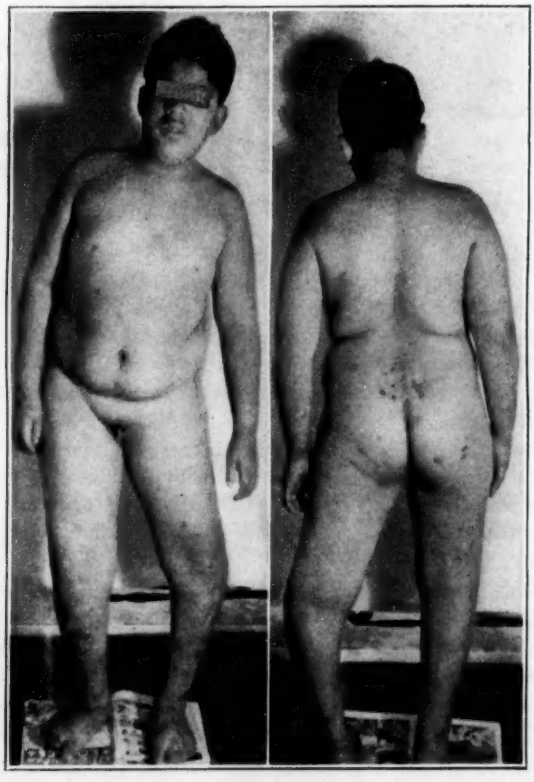

Fig. 1.—Photographs of the patient, showing girdle obesity, genital infantilism and bowing of the left leg (genu varum).

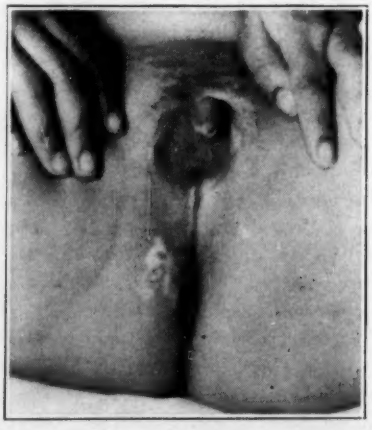

Fig. 2.—Photograph of the perineum, showing the underdeveloped penis and the very small, empty scrotum. Note areas of leukoderma near the anus.

The hands were short and thick, but the fingers tapered somewhat. On the lateral aspect of the base of the right little finger there was an operative scar left by the removal of an extra digit. The thighs and buttocks were thick and covered by considerable subcutaneous fat. The left lower extremity was shorter than the right and showed pronounced lateral bowing (fig. 1). The feet were short, thick and broad; the left was the smaller of the two. The lateral aspect of each foot exhibited an old scar resulting from the removal of an extra digit. The gait was characterized by a limp which favored the shortened left leg. The reflexes were physiologic, and there were no gross abnormal neurologic findings. The measurements were as follows: (*a*) weight, 123 pounds (55.9 Kg.); (*b*) height, 56 inches (142 cm.); (*c*) circumference of head, 19 inches (48 cm.); (*d*) left anterior superior iliac spine to left internal malleolus, 29 inches (74 cm.); (*e*) right anterior superior iliac spine to right internal malleolus, 31½ inches (80 cm.); (*f*) umbilicus to left internal malleolus, 31½ inches (80 cm.); (*g*) umbilicus to right internal malleolus, 32½ inches (82.5 cm.).

Laboratory Findings.—The blood counts were normal. The Hinton and Eagle reactions of the blood were negative. Microscopic, chemical and volume urinalyses gave normal results. Chemical study of the blood showed: nonprotein nitrogen,

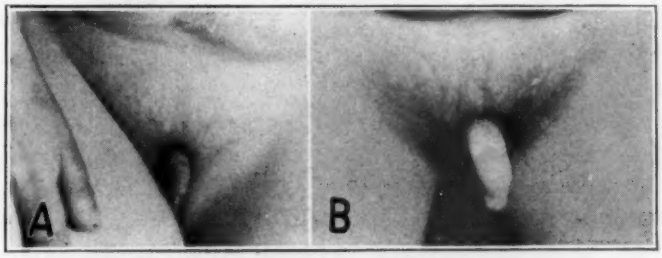

Fig. 3.—*A*, photograph showing slight increase in growth of pubic hair following administration of 16,000 rat units of chorionic gonadotropin. The penis and scrotum remain small and the testes undescended. *B*, photograph showing increased growth of the penis and of pubic hair following the administration of testosterone propionate. The testes have now reached the bottom of the scrotum.

20 mg., per hundred cubic centimeters; creatine, 1 mg.; cholesterol, 163 mg.; calcium, 10.2 mg., and phosphorus, 4.5 mg.

A dextrose tolerance test (after administration of 50 Gm. of dextrose orally) gave the following results (amount of dextrose per hundred cubic centimeters of blood): fasting specimen, 80 mg.; thirty minutes, 110 mg.; sixty minutes, 133 mg., and ninety minutes, 100 mg.

The basal metabolic rate, as determined on three occasions, was —11, —10 and —6 per cent (Benedict standard).

A psychometric test (Stanford-Binet test performed by Dr. F. P. Watts, psychologist) gave the following results: chronologic age, 12 years 2 months; mental age, 5 years 4 months; intelligence quotient, 44. A second test, performed at the termination of treatment, gave an intelligence quotient of 42.

Roentgenograms made in 1935 (fig. 4) showed bifid fifth metatarsals, thus accounting for the six toes on each foot. A similar defect was observed in films of the right hand. The sella turcica was roentgenographically normal. The skeletal and chronologic ages compared favorably. The roentgenogram of the left leg revealed lateral bowing of the tibia, the proximal epiphysis of which apparently

had rotated and slipped forward on the head of the shaft. Hypertrophic changes were noted in this epiphysis, accompanied by some sclerosis along the epiphysial line of the tibial shaft. The roentgenologist (Dr. J. L. Martin) postulated a preceding traumatic epiphysitis which had partially healed with resultant deformity (genu varum).

Course.—In January 1940 one of us (P. T. J.) performed an osteotomy on the left tibia for correction of the genu varum deformity. Specimens of bone removed at operation were examined by Dr. R. S. Jason, pathologist, who reported that gross and histologic study revealed normal osseous tissue.

After the patient's recovery from the operation a 1,200 calory diet was prescribed; however, difficulty was experienced in keeping him on this dietary regimen. Beginning on February 17, 1940, the patient received 3 cc. (100 rat units per cubic centimeter) of chorionic gonadotropin (antuitrin-S, Parke, Davis & Co.) subcutaneously three times a week for a period of four and a half months. The only

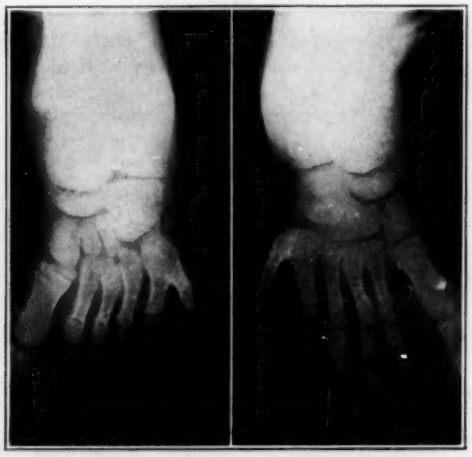

Fig. 4.—Roentgenogram of the feet, visualizing the bifid metatarsal (fifth) bones from which the supernumerary toes arise.

significant objective result of this therapy was a moderate growth of pubic hair. The size of the penis and of the scrotum remained unchanged and the testes undescended (fig. 3 *A*).

The administration of gonadotropin was discontinued, and in July 1940 testosterone propionate was administered intramuscularly in doses of 25 mg. three times per week for a period of two months. After the patient had received 300 mg. it was observed that the penis (fig. 3 *B*) had increased in length from 1 inch (2.5 cm.) to 1½ inches (3.8 cm.). The scrotum was also slightly larger and congested. For the first time one was able to palpate small atrophic testes in the bottom of the scrotum. However, no apparent improvement was observed in the patient's eyesight or mentality.

COMMENT

The patient presented the classic cardinal signs of girdle obesity, mental deficiency, hypogenitalism, polydactylism, familial occurrence and ocular defects (strabismus, nystagmus, myopia and pigmentary

chorioretinal degeneration). In addition there were present associated anomalies, namely, impairment of hearing, flattening of the occiput, hypoplasia of the mandible, a high-arched palate, dental malocclusion, genu varum and shortness of the hands and feet. The patient's 20 year old brother apparently presented an incomplete variety of the same syndrome. Weiss [2a] and other authors have reported atypical forms in which nerve deafness appeared to act as a mutual equivalent or substitute for retinitis pigmentosa.

The etiology of the symptom complex remains a subject of controversy. Raab's [7] theory that the condition results from hypothalamic dysfunction caused by a blocking off of secretion from the pars intermedia by a high and massive dorsum sellae is no longer tenable. In reported cases the sella turcica is generally described as being roentgenographically normal. Moreover, recent studies [8] disprove the theory of pituitary drainage into the hypothalamus. Biedl's original hypothesis, that the syndrome was a familial form of dystrophia adiposogenitalis of cerebral rather than of pituitary origin, is still generally accepted.

Ornsteen [9] suggested that the association of adiposogenital dystrophy, mental deficiency and retinitis pigmentosa (anomalies of epiblastic origin) is due to a developmental defect of the ectopic zone of the prosencephalon. He attributed the skeletal defects (mesoblastic origin), such as polydactylism, to accidental coupling of defective somatic genotypic characters with cerebral unit characters. A modification of Ornsteen's theory has been advanced by Jenkins [10] and Cockayne,[11a] and their associates. These writers have stated that the hereditary developmental defects of mesodermal and ectodermal origin are recessive and are due to the mutation of two genes in the same chromosome.

The few available postmortem records [11] have contributed little thus far toward elucidation of the primary causation. Riggs,[12] who studied the brain histologically in 2 cases of this syndrome, found evidence in the

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7. Raab, W.: Klinische und röntgenologische Beiträge zur hypophysären und zerebralen Fettsucht und Genitalatrophie, Wien. Arch. f. inn. Med. **7**:443, 1924; cited by Jenkins and Poncher.[10]

8. Wislocki, J. B., and King, L. S.: The Permeability of the Hypophysis and Hypothalamus to Vital Dyes, with a Study of the Hypophyseal Vascular Supply, Am. J. Anat. **58**:421, 1936.

9. Ornsteen, A. M.: A Contribution to the Pathogenesis and Heredity of the Laurence-Biedl Syndrome, Am. J. M. Sc. **83**:256, 1932.

10. Jenkins, R. L., and Poncher, H. G.: Pathogenesis of the Laurence-Biedl Syndrome, Am. J. Dis. Child. **50**:178 (July) 1935.

11. (*a*) Rathmell, T. K., and Burns, M. A.: The Laurence-Biedl Syndrome Occurring in a Brother and Sister, Arch. Neurol. & Psychiat. **39**:1033 (May) 1938. (*b*) Sorsby, A.; Avery, H., and Cockayne, E. A.: The Laurence-Moon-Biedl Syndrome, Quart. J. Med. **8**:55, 1939.

12. Riggs, H. E., in discussion on Rathmell and Burns.[11a]

cerebral cortex and the brain stem of widespread intrauterine arrest in development. Congenital defects in the medial coat of the blood vessels supplying the region of the hypothalamus were demonstrated in both cases.

Some writers [13] have reported improvement in the vision and mentality of patients with this syndrome, as well as loss of weight and increased genital development, following the administration of pituitary, thyroid and gonadal extracts. However other workers [14] have employed similar therapy without demonstrable change in the patient's condition except perhaps for genital response.

Except for a sparse growth of pubic hair the patient whose case is reported here showed no response to 16,000 rat units of chorionic gonadtropin. This lack of response can hardly be attributed to inadequate dosage. Bigler, Hardy and Scott [15] observed that if an undescended testicle was going to descend it would do so after 1,000 to 8,000 rat units of gonadotropin had been given. Nixon [16] found the effective dosage to range between 7,500 and 15,000 rat units as a rule.

Chorionic gonadotropin works in cryptorchidism by stimulating the interstitial cells of Leydig in the testis to produce androgen. The failure of the stimulating material (chorionic gonadotropin) and the success of replacement therapy (testosterone) in evoking development of secondary sex characteristics in this case is best explained on the basis that the testes were unable to manufacture adequate amounts of androgen. That on descent the testes were found to be very small and atrophic is additional evidence of their hormonal insufficiency.

It has been demonstrated [17] that undescended abdominal testes secrete considerably less androgen than scrotal testes. The apparent testicular insufficiency may be variously attributed to such possible factors as atrophy secondary to pituitary deficiency, harmful effect of the abdominal temperature and primary congenital hypoplasia. Unfortunately facilities were not available for making a quantitative analysis of the patient's urine for androgen.

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13. Weiss, E.: Cerebral Adiposity with Mental Deficiency and Retinitis Pigmentosa: The Laurence-Biedl Syndrome, Endocrinology **15**:435, 1931. Reilly and Lisser.[1d]

14. Warkany, Frauenberger and Mitchell.[1b] Marmor and Lambert.[1c] Jenkins and Poncher.[10]

15. Bigler, J. A.; Hardy, L. M., and Scott, H. V.: Cryptorchidism Treated with Gonadotropic Principle, Am. J. Dis. Child. **55**:273 (Feb.) 1938.

16. Nixon, N.: The Undescended Testicle, Am. J. Dis. Child. **55**:1037 (May) 1938.

17. Hanes, F. M., and Hooker, C. W.: Hormone Production in the Undescended Testis, Proc. Soc. Exper. Biol. & Med. **35**:549, 1937.

Heckel [18] and others have observed that the administration of androgen may damage the seminiferous tubules; hence its use should be restricted to cases in which both testes are incapable of responding to stimulation therapy. Finally, in view of the irreparable mental deficiency component in the Laurence-Moon-Biedl syndrome, androgenic therapy capable of causing subjective and objective sexual excitation should be administered with discretion. In these unfortunate patients cryptorchid sterility is perhaps a virtue which should not be disturbed. Not all affected persons are sterile. Direct inheritance of the full syndrome has been reported [11b] in only 1 possible instance; however, many reports give histories suggestive of the partial presence of the syndrome in ascendants and their relatives.

SUMMARY

A case of the Laurence-Moon-Biedl syndrome in a Negro boy is described.

The patient's cryptorchidism was not affected by the administration of chorionic gonadotropin but responded to treatment with androgen (testosterone propionate).

Contrary to reports in the literature, no improvement was noted in the patient's vision or mentality after endocrine therapy.

Because of the association of irreparable mental deficiency with hypogenitalism in patients with this syndrome, the sex-exciting endocrine principles have very limited practical usefulness for these patients and should not be used without discretion.

The testosterone propionate used in this case was supplied by the Schering Corporation, Bloomfield, N. J.

520 W Street, N.W.

18. (*a*) Heckel, N. J.: Production of Oligospermia in a Man by the Use of Testosterone Propionate, Proc. Soc. Exper. Biol. & Med. **40**:658, 1939. (*b*) Moore, C. R.: Physiology of the Testes and Therapeutic Application of Male Hormone, Bull. New York Acad. Med. **16**:135, 1940. (*c*) Thompson, W. O., and Heckel, N. J.: Male Sex Hormone: Clinical Applications, J. A. M. A. **113**:2124 (Dec. 9) 1939.

A RARE SYNDROME OF BAND-SHAPED KERATITIS AND ARTHRITIS

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Band-shaped opacity of the cornea is a rare disease, first described by Dixon,[1] in his textbook on diseases of the eye in 1848, as a "curious form of opacity depending upon the spontaneous deposit of earthy salts between the epithelium and the anterior surface of the cornea." Dixon therefore named this condition "calcareous film of the cornea."

Since Dixon's report, the literature has added little to the knowledge of this condition. However, as more cases were recognized it became apparent that this disease is of several types.[2] By far the most common type is seen in old people, usually with sightless, degenerated and often shrunken eyes, the result of long-standing iridocyclitis due to any of a number of causes, including glaucoma and sympathetic ophthalmia. Occasionally it occurs in an elderly person with otherwise normal eyes. The pathogenesis of this type is probably a degenerative process associated with advancing age. Less commonly, the opacity follows severe interstitial keratitis or long-standing mechanical irritation of the cornea. By far the most rare type of this disease is that described as occurring in children, which is almost constantly (19 of 24 reported cases) associated with arthritis of some degree and a quiet, chronic, nondisorganizing uveitis. The first example was reported by Ohm in 1910.[3] Since the entire literature includes only 24 cases of this type of opacity and the American literature only 1,[4] it may be of interest to report a case we have recently observed.

REPORT OF A CASE

The patient was a 4 year old girl whose past history, except so far as it relates to the present illness, was uneventful. The family history was unimportant, and there was no known exposure to tuberculosis. At the age of 13 months, after

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From the Pediatric Service (Dr. Béla Schick, Director) of the Mount Sinai Hospital.

1. Dixon, J.: A Guide to the Practical Study of Diseases of the Eye, London, J. Churchill, 1848, p. 114.

2. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 2010.

3. Ohm, J.: Bandförmige Hornhauttrübung bei einem neunjährigen Mädchen, Klin. Monatsbl. f. Augenh. **48**:243-246, 1910.

4. Wong, R. T.: Band-Shaped Opacity of the Cornea Associated with Juvenile Atrophic Arthritis: Report of a Case, Arch. Ophth. **26**:21-24 (July) 1941.

she had been toddling normally for about one month, the patient sustained a fall in which she struck her right knee. Shortly thereafter, the knee became swollen and her right leg was held flexed with the toes turned outward. She was generally afebrile, although occasionally her temperature rose to 100 F. The knee was not red or hot and was only moderately tender. When she was 1½ years of age, roentgen examination of the right knee was reported as showing possible tuberculosis. Since permission for exploration was refused, a brace which prevented flexion of the knee was applied and worn until she reached the age of 3 years. Moderate puffiness of the right knee persisted, with exacerbations lasting one to two weeks.

Six months before her admission to the hospital roentgenograms of the legs and chest were reported as normal. At about this time, limitation of motion of the right arm was noted. She was treated with twelve weekly doses of 600,000 U. S. P. units of vitamin D, under which therapy the right arm and knee seemed to improve. Likewise, there appeared to be some improvement with heliotherapy during the last summer before her admission.

During the three months preceding admission, the child complained of pains in the joints of her legs, which became stiff. She cried out with pain in her knees at night, and on awakening her knees were spastic in partial flexion, requiring several minutes of painful effort for the child to extend them.

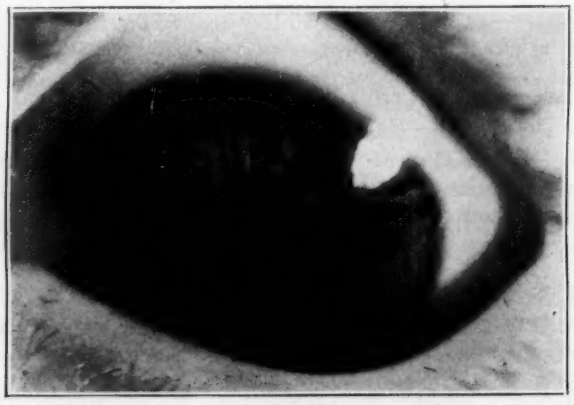
Three months before her admission, it was noted that the child had photophobia of the left eye and a film over this eye. This lesion had been apparently static.

On physical examination, the child was a chubby, well developed and well nourished 4 year old girl. She walked holding her right knee stiffly and with the arch of her back exaggerated. She preferred not to walk at all and grasped objects for support every few steps. When standing still, she could and did flex both hips and knees.

Ocular examination by Dr. David Wexler, of the ophthalmologic service, gave the following results: The right eye was normal. The left eye revealed a transverse band of grayish yellow opacification about 4 mm. in width, extending across the cornea in the palpebral fissure just below the equator to just short of the limbus on either side (photograph). Its borders were sharply defined. Close inspection revealed that the opacity contained closely grouped yellowish punctate dots and dark clear spaces, both clefts and punched-out areas. The opacities appeared to be superficial, immediately under the epithelium, which was finely humped over them. Slit lamp examination could not be performed because of the patient's lack of cooperation. The pupil was small and irregular and enlarged only slightly on dilation; there were posterior synechias at many points. Vision was definitely present, but the fundus reflex was faint, owing to the opacity. The fundus was not well made out because of the corneal opacity.

The pharynx revealed hypertrophied lymphoid tissue. Examination of the chest showed it to be normal. On abdominal examination, the liver was felt at the costal margin and the spleen was not palpable. There was no lymphadenopathy. Examination of the extremities revealed atrophy of the calf muscles on both sides, more on the right. There was limitation of flexion and extension of the right knee, which extended to only 170 degrees, and of the right elbow, which extended to only 135 degrees. There was also a suggestion of limitation of motion of the right hip, with a positive Patrick sign, although the head of the femur moved freely in the socket. There was soft tissue enlargement about both knees, more marked on the left. There was no involvement of other joints.

Laboratory examination revealed no anemia but a moderate leukocytosis, with a white cell count of 14,000 with 67 per cent polymorphonuclear cells. The urine contained 1 to 5 white blood cells and a rare red blood cell per high power field. Tuberculin (patch and Mantoux) tests gave negative results, as did also a cutaneous test with undulant fever vaccine. The reaction to the Schick test was positive. Kahn, Wassermann, and brucella and paratyphoid agglutination tests were negative. An electrocardiogram and a roentgenogram of the chest were within normal limits. Roentgenograms of the knees revealed some soft tissue swelling and slight periarticular atrophy but no distinct bony abnormality. The concentrations of urea nitrogen, sugar, uric acid and total protein in the blood were normal. The phosphorus content was also normal on two occasions, 4.1 and 4.2 mg. respectively per hundred cubic centimeters of blood, and the phosphatase content was 22 King-Armstrong units per hundred cubic centimeters (high normal). The calcium content of the blood, however, was elevated on the two occasions it was determined, being 12.1 and 12.7 mg. per hundred cubic centimeters. Qualitative tests for urinary excretion of calcium showed the amount to be elevated. The erythrocyte sedimentation time was thirty minutes for 18 mm., which is considerably more rapid than normal.



Photograph of the left eye, showing the band-shaped opacity.

The course in the hospital was altogether uneventful, the temperature never having risen above 100 F. The child was apparently free of pain. Her condition at discharge was unaltered.

COMMENT

Band-shaped opacity of the cornea when fully developed has an appearance similar to that described in our case, regardless of causation.[5] However, the condition is usually bilateral, developing first in one eye and then the other. Its development is never accompanied by more than slight irritation and pain due to the corneal irregularity produced by the

5. Fuchs, E.: Textbook of Ophthalmology, New York, D. Appleton and Company, 1899, p. 209.

underlying deposits. Most commonly, the only symptom is gradual blurring of vision if sight has been previously present.

The first objective change [6] is revealed by slit lamp examination. It consists of a slight turbidity at the level of Bowman's membrane, in which are distinguishable dark round holes. These are pathognomonic months or even years before a macroscopically visible opacity develops. Such changes might have been found in the right eye of the patient under discussion had she submitted to slit lamp examination. It is possible also that incipient corneal opacification might be much more commonly found in association with juvenile arthritis if all children with Still's disease were subjected to slit lamp examination.

The macroscopic lesion may begin in the center and progress peripherally, but more commonly it begins at the two edges and progresses toward the center. Development of the lesion is very slow, often occupying a span of years.

Pathologic examination [7] reveals the first change to be a granular or hyaline deposition on the surface of Bowman's membrane, with eventual degeneration, irregular thickening and fibrosis of the membrane and the superficial layers of the substantia propria. In this matrix, calcium salts are irregularly deposited. Foreign body giant cells are commonly found. The brittle Bowman's membrane cracks readily, and portions of it may fall out altogether, thus accounting for the transparent clefts previously described.

Chemical studies [8] reveal the presence of calcium phosphates and carbonates in large amounts and of sulfur and silicon in small amounts.

Of the pathogenesis and causation of band-shaped keratitis in children, nothing is known. Its almost constant association with arthritis suggests that Still's disease either is the cause of or is caused by the same agent as the keratitis. However, this merely relates the disease to another of equally obscure origin. It has been suggested that Still's disease may be due to disturbed parathyroid activity.[9] Such a theory would account for the elevated blood calcium content in the present case, the deposition of calcium salts in the cornea and even the apparent beneficial influence of vitamin D therapy in counteracting mobilization of calcium from the bones. However, the normal phosphatase level

6. Koby, F. E.: Slitlamp Microscopy of the Living Eye, translated by C. Goulder and C. L. Harris, Philadelphia, P. Blakiston's Son & Co., 1925.

7. von Hippel, E.: Bandförmige Hornhauttrübung, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 11, pt. 1, p. 294.

8. Sisson, R. J.: Band Keratitis, Am. J. Ophth. **17**:222-224, 1934.

9. Moncrieff, A. A.: Arthritis in Children, in Rolleston, H.: British Encyclopaedia of Medical Practice, London, Butterworth & Co., Ltd., 1936, vol. 2, pp. 113-119.

practically rules out hyperparathyroidism. Furthermore, while lenticular opacities are described, band-shaped keratitis is not described as occurring in frank hyperparathyroidism. Nevertheless, while the hypercalcemia cannot be considered causative, it is not unlikely that it contributed to, or at least accelerated, the opacification in the present case. To account for the hypercalcemia one may perhaps implicate the massive dose therapy with vitamin D which the child received up to three months before admission. Vollmer [10] has shown that vitamin D is stored in the skin, liver and brain, and it may be that sufficient amounts continue to be liberated to maintain the blood calcium above normal. If this is so, the hypercalcemia is of recent origin, and it may be more than a coincidence that the visible opacification occurred shortly after the institution of the vitamin D therapy. The arthritis and the tendency to band-shaped keratitis may have already existed in this case when the hypercalcemia was induced by vitamin D therapy, and the hypercalcemia may have merely accelerated the deposition of calcium salts in the already incipient opacity.

I suggest as a possible pathogenesis of the syndrome described a common reaction of the uveal tract, cornea and synovia to a noxious agent, possibly the hemolytic streptococcus.[11] The uveitis in turn may affect the nutrition of the cornea, a disturbance which may well play a role in the development of the band opacity, as evidenced by the experimental work of von Hippel,[7] who produced the condition experimentally in rabbits twenty days after ligation of the vortex veins. The doubly injured cornea is thus made more susceptible to the slight traumas to which it must be constantly exposed. As a result, it undergoes degenerative changes, with subsequent deposition of calcium salts, which in the case reported here may have been accelerated by the therapeutically induced hypercalcemia.

Treatment of band-shaped opacity of the cornea is of course called for only when vision is otherwise intact. Even under such circumstances treatment should be postponed until the opacity becomes hard and flaky. At this stage, it may fall off spontaneously in sufficiently large pieces to permit good vision or may be removed with a sharp spud. If removal by abrasio corneae can be effected, relatively clear cornea remains underneath and there is no tendency to recurrence. Also sug-

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10. Vollmer, H.: Distribution of Vitamin D in Body After Administration of Massive Doses, Am. J. Dis. Child. **57**:343-348 (Feb.) 1939.

11. Dawson, M. H.; Olmstead, M., and Boots, R. H.: Studies on Etiology of Rheumatoid Arthritis: Agglutination Reaction with Hemolytic Streptococci in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **28**:421-422, 1930. Eagles, G. H.: Acute Rheumatic Fever and Rheumatoid Arthritis as Virus Diseases, Proc. Second Internat. Cong. Microbiol., 1936, pp. 84-85. Dawson, M. H.: Rheumatoid Arthritis, in Nelson New Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1935, vol. 5, pp. 626-630.

gested are optical iridectomy,[12] attempted solution of the incrustation by bathing the eyes with any one of a number of solvents, including acetic, tartaric, nitric and hydrochloric acids [13] and neutral ammonium tartrate solution,[14] subconjunctival injection of potassium iodide,[3] roentgen therapy [15] and diets rich in citrous fruits. The best treatment, however, still remains Dixon's original surgical removal.

SUMMARY

The general subject of band-shaped keratitis is briefly reviewed.

A case of band-shaped opacity of the cornea in a 4 year old girl associated with low grade iridocyclitis and chronic arthritis is presented.

The pathology, chemistry and treatment are reviewed, and theories of pathogenesis are discussed.

12. von Graefe, A.: Beiträge zur Pathologie und Therapie des Glaucoma, Arch. f. Ophth. (pt. 3) **15**:138-148, 1869. Landesberg: Two Cases of Ribbon-Shaped Corneal Opacity, Complicated with Intraocular Changes, Arch. Ophth. **3**:63-70, 1873.

13. Nettleship, E.: On a Rare Form of Primary Opacity (Transverse Calcareous Film) of the Cornea, Arch. Ophth. **8**:293-319, 1879. Galezowski, X.: Sur la dégénérescence calcaire de L'épithélium cornéen et sur son traitement, Rec. d'ophth. **13**:321-333, 1881. Sommer, I.: Ein Fall von primärer gurtelförmiger Hornhauttrübung, Ztschr. f. Augenh. **55**:352-354, 1925. Francois, J.: De l'opacité en ceinture et de son traitement, Bull. Soc. d'opht. de Paris, 1934, pp. 636-642.

14. zur Nedden: Ueber Schädigung der Hornhaut durch Einwirkung von Kalk, Arch. f. Ophth. **63**:319-338, 1906.

15. Merkulow: Physikalische Methoden der Behandlung der bandförmige Hornhauttrübung, Ztschr. f. Augenh. **67**:73-78, 1929.

Progress in Pediatrics

OSTEODYSTROPHIA FIBROSA COMBINED WITH PRECOCIOUS PUBERTY AND EXOPHTHALMIC GOITER

PATHOLOGIC REPORT OF A CASE

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The bizarre syndrome characterized by severe, often asymmetric, disease of bones, melanotic pigmentation and precocious puberty in females has in recent years received considerable attention in the medical literature. A similar syndrome, but without precocious puberty, occurs, less frequently, in males. At present about 26 probable cases are reported, although a large number of less obvious cases undoubtedly exists. The literature on the subject has been reviewed by Albright and co-workers [1] and by McCune and Bruch.[2] Since the publication of these reviews several other cases have been reported, among them those of Mondor and co-workers,[3] Braid,[4] Robson and Todd,[5] Diez [6] and Sum-

From the Laboratory Division, Montefiore Hospital.

1. (*a*) Albright, F.; Butler, A. M.; Hampton, A. O., and Smith, P.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females, New England J. Med. **216**:727-746 (April 29) 1937. (*b*) Albright, F.; Scoville, W. B., and Sulkowitch, H. W.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation, and Gonadal Dysfunction: Further Observations Including Report of Two More Cases, Endocrinology **22**:411-421 (April) 1938.

2. McCune, D. J., and Bruch, H.: Osteodystrophia Fibrosa: Report of Case in Which Condition Was Combined with Precocious Puberty, Pathologic Pigmentation of Skin and Hyperthyroidism, with Review of Literature, Am. J. Dis. Child. **54**:806-848 (Oct.) 1937.

3. Mondor, H.; Ducroquet, R.; Leger, L., and Laurence, G.: Sur un cas d'ostéite fibro-kystique unilaterale avec pigmentation et puberté précoce, Rev. gén. de clin. et de thérap. **52**:823-824 (Dec. 10) 1938; Un cas d'ostéite fibro-géodique disséminée avec pigmentation cutanée et puberté précoce, J. de chir. **53**:593-624 (May) 1939.

(Footnotes continued on next page)

merfeldt and Brown.[7] Unfortunately adequate postmortem material does not exist, although in the discussion by Musser and Barnwell of the paper of Albright's group [1b] there is a brief mention of an incomplete autopsy on a male patient who died after thyroidectomy. As far as we are aware, ours is the first complete pathologic report of such a syndrome.

The clinical data on this case have already been reported in the excellent, comprehensive clinical review by McCune and Bruch. The pathologic observations which we present, while in no wise elucidating the fundamental pathogenesis, offer many suggestive leads. The study of such cases, we feel, is more than merely an exercise in medical esoterica, for in a sense the cases represent preformed biologic experiments, the unraveling of which may furnish valuable data on certain endocrine interrelationships.

REPORT OF CASE

CLINICAL HISTORY

The clinical history of this case, reported in detail by McCune and Bruch,[2] is summarized here.

The child was the first of nonrelated, young Jewish parents, born Sept. 9, 1926 at term and delivered spontaneously after a moderately severe labor. The birth weight was 7 pounds 8 ounces, and the condition was good. During the first few days of life intense jaundice developed, but it subsided after an indeterminate period. Physical development seemed to progress normally, and the child began to walk at 14 months. When she was 2 years old, the parents suddenly became aware of numerous irregularly shaped patches of brownish pigmentation of her skin, and without warning she began to have irregular uterine bleeding, the breasts enlarged and a sparse growth of axillary and pubic hair appeared, so that at the age of 4 years she was sexually mature, although her mental development remained consistent with her chronologic age. Since she was 1 year old the parents had noted a progressive bowing of the legs, which impeded locomotion and required a corrective operation at the age of 3. At the age of 3 years and 5 months she fractured her right femur (the first of a series of pathologic fractures). At 4 the lower extremities were extremely deformed, the gait clumsy and waddling and unassisted locomotion impossible. At the age of 4 years and 7 months, she was

4. Braid, F.: Osseous Dystrophy Following Icterus Gravis Neonatorum: Generalized Osteitis Fibrosa with Areas of Pigmentation of Skin and Precocious Puberty in Female, Arch. Dis. Childhood **14**:181-202 (Sept.) 1939.

5. Robson, K., and Todd, J. W.: Fibrocystic Disease of Bone with Skin Pigmentation and Endocrine Dysfunction, Lancet **1**:377-380 (Feb. 18) 1939.

6. Diez, J.: La ostéitis fibrosa diseminada con pubertad precoz y pigmentaciones cutáneas (síndrome de Albright), Prensa méd. argent. **26**:1870-1897 (Sept. 27) 1939.

7. Summerfeldt, P., and Brown, A.: Osteodystrophia Fibrosa, Am. J. Dis. Child. **57**:90-101 (Jan.) 1939.

treated at Babies Hospital because of another fracture of the right femur. On physical examination she was well nourished, mentally alert, 112 cm. tall and weighed 22 Kg. Sexual maturity appeared complete. The uterus was estimated about 5 cm. long, the cervix about 1 cm. long and the ovaries 2 cm. in diameter. The complexion was swarthy; the skin was of delicate texture, warm and moist, and scattered diffusely over the body were irregularly outlined patches of coffee-colored pigment anteriorly and posteriorly, more profuse on the left than on the right side. The skeleton was deformed. The head was larger than normal, the left maxillary region more prominent than the right. The right femur curved laterally, and the right leg was shorter than the left. There were no features suggestive of acromegaly. Dentition was accelerated; most of the teeth belonged to the permanent set, irregularly arranged and carious. The lungs and heart, except for a soft systolic murmur over the entire precordium, were normal. The blood pressure was 110 systolic and 60 diastolic. The pulse was rapid and bounding, with a rate of 120 per minute. The edge of the liver was just palpable, and the spleen was felt 2 cm. below the costal margin. Both kidneys were palpable. The thyroid was not felt. Neurologic examination gave negative results. Laboratory examination likewise revealed nothing of significance except an elevated basal metabolic rate, 34 per cent above the normal according to the Talbot, Wilson and Worcester standards based on weight alone. The roentgen findings were interpreted as those of a generalized systemic disease of the skeleton with cystlike rarefaction of the bones associated with varying degrees of osteoporosis and osteosclerosis, deformities of outline and architecture of the bones, especially of the long bones, asymmetric in distribution and more extensive on the right side. A descriptive diagnosis of osteodystrophia fibrosa, possibly of the von Recklinghausen variety, was made. There were areas of diminished density producing a mottled moth-eaten appearance in the skull, and the similarity of these changes to those of Paget's disease was stressed. Lesions were also present in the ribs, especially those of the left half of the thorax, spine, scapulas and right innominate bone. The zones of preliminary calcification were intact. There was precocious development of the centers of ossification, and the skeletal age was estimated at 10 to 12 years. While in the hospital the child exhibited emotional instability, diaphoresis and slight tachycardia.

In the following five years the child sustained nineteen recognized fractures of the right half of the skeleton, the bones uniting within four to six weeks. There was progressive deterioration of the skeleton with increasing deformity of stature. The skeletal development in October 1935, when the patient was 9 years and 1 month old, was that of a woman of 18 to 22. Roentgen examination revealed progression of the osseous lesions with involvement of the clavicles and left arm, and collapse of several spinal vertebrae. Only the left femur appeared to be approximately normal. By the fifth year the thyroid gland had become easily palpable and nervousness and sweating were more prominent. The blood pressure was 150 systolic and 50 to 60 diastolic, tachycardia persisted, and the basal metabolic rate had risen to + 44 per cent. At 9 years the hyperthyroidism was obvious. There was no exophthalmos. The basal metabolic rate was + 65 per cent by the Talbot-Wilson standards. Respirations were rapid and shallow and vital capacity diminished. Menstruation appeared more regularly, at intervals of six to eight weeks,

lasting three to five days, with a moderate loss of blood. On two occasions there were metrorrhagia, but never menorrhagia.

In May 1936, at the age of 9 years and 8 months, physical findings were about the same as on previous occasions, except that the eyes were now slightly prominent and there was a slight lid lag. Neurologic examination gave negative results. On the Terman, Goodenough and Stanford-Binet tests the mental age was 7 years and 5 months. Additional laboratory examinations revealed urine of high specific gravity with occasional faint traces of albumin and a reducing substance in a concentration sometimes as high as 4 plus. Bence Jones protein was absent. Blood chemistry values were within normal limits.

Studies of the calcium balance were done when the child was 5 years old, 5 years and 6 months, and 9 years and 2 months; they gave results similar to those obtained for normal children. The calcium and phosphorus balance was positive. When parathyroid extract was administered daily for five days, the balance became negative by the third day and remained negative for more than a week after the last injection.

The neck was explored for parathyroid tumor when the patient was 7 years old, and a nodule removed from the lower pole of the left lobe of the thyroid gland proved to be thyroid tissue showing adenomatous hyperplasia. In November 1935, when the child was 9 years and 2 months old, bone was obtained from the anterior aspect of the right femur for biopsy. The fragment of bone removed was composed of soft pieces of calcified bone, gray cartilage and bright red marrow, and microscopically it showed numerous imperfect trabeculae composed of osteoid tissue, or bone surrounded by osteoid, a moderate number of osteoblasts about the trabeculae, and, except at the periphery of a mass of hyaline cartilage, very few osteoclasts. Islands of calcium were present in the cartilage and in the osteoid tissue which surrounded it. The surface of the cartilage was covered with osteoid. The marrow was replaced by dense collagenous connective tissue which contained numerous multinucleated giant cells. The cortical bone was thin and irregular; it contained an abundance of calcium, and the haversian canals were wide and filled with connective tissue.

In June 1933, when the child was almost 7 years old, serial twenty-four hour specimens of urine were examined for estrogenic and gonadotropic substances. On three occasions she excreted more than 4 rat units daily of estrogen. Gonadotropin was absent from all except one specimen, in which it appeared in high concentration and was thought to represent the occurrence of ovulation. In May 1936, when she was 9 years and 8 months old, two specimens of urine were examined; one contained 16 rat units and the other more than 96 rat units of estrogen per liter. (Four rat units of estrogen is considered the average daily excretion of an adult woman.)

Microscopic examination of a piece of skin showed granular brown pigment in the basal layers of the epidermis and normal nerve fibers.

During a short study made while the patient was on an ample diet, she was found to excrete 0.4 Gm. of creatinine and 0.45 Gm. of creatine in twenty-four hours. The creatinine coefficient was 6.6 mg. Of 1 Gm. of creatine administered by mouth, 31 per cent was excreted as creatine in the first twenty-four hours and 8 per cent during the next twenty-four hours.

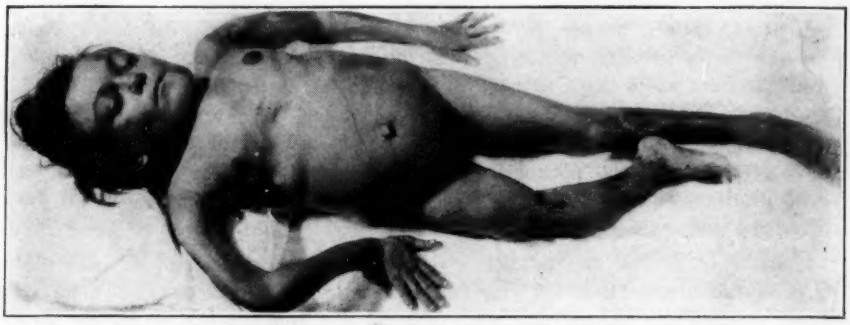

Fig. 1.—The patient in 1937 (chronologic age, 11 years). Note the sexual development, skeletal deformity and areas of pigmentation.

Fig. 2.—The right arm in 1937 (chronologic age, 11 years). There are expansion of the medullary canal, diffuse osteoporosis with numerous cystlike spaces, and marked deformity—the result of pathologic fractures.

Further History Since the Report of McCune and Bruch.—The child was admitted to Montefiore Hospital in October 1937, when she was 11 years old. There were no additional notable physical findings. It was thought that the lymph nodes were generally slightly enlarged and nontender, the cartilage of the nose and ears harder than usual, and the peripheral vessels palpably sclerosed. The liver was palpable 4 fingerbreadths below the right costal margin and the spleen 3 fingerbreadths. The blood pressure was 120 systolic and 70 diastolic, the pulse rate 130 and the respiratory rate 36. The pulse and the respiratory rate were

Fig. 3.—The left arm, showing lesions similar to those in the right arm, though less extensive.

always elevated, and the patient perspired freely all the time. There was a solemn adult expression on the face of the child, and mental development seemed compatible with her limited education.

Laboratory examination gave no new information. The hemoglobin concentration was 91 per cent, the red blood cell count 4,270,000 and the white blood cell count 11,500, with polymorphonuclear cells 38 per cent, lymphocytes 50 per cent, monocytes 5 per cent and eosinophils 7 per cent. The blood smear showed no unusual cells.

Chemical examination of the blood revealed the following values: dextrose, 81 mg. per hundred cubic centimeters; urea nitrogen, 11.7 mg.; calcium, 9.6 mg.; phosphorus, 2.3 mg.; cholesterol, 134 mg.; cholesterol esters, 84 mg.; albumin, 3.1 Gm.; globulin, 3.0 Gm.; phosphatase, 0.21 unit (Kay's); chlorides, 602 mg. The icteric index was 6. A dextrose tolerance test showed the following values for blood sugar: fasting, 89 mg. per hundred cubic centimeters; one-half hour, 172 mg.; one hour, 185 mg.; two hours, 164 mg.; three hours, 92 mg.; four hours, 89 mg.

Fig. 4.—The right leg in 1937 (chronologic age, 11 years), showing almost complete destruction of the architecture.

A Friedman rabbit ovulation test gave a negative result.

The urine contained dextrose in amounts varying from a trace to 2.2 per cent.

The basal metabolic rate (on different determinations) was + 92, + 120 and + 112.

A Hamilton test gave a negative result.

The course was uneventful until December 1937, when acute abdominal pain developed and a mass was noted in the right lower quadrant of the abdomen.

Laparotomy disclosed torsion of a cystic right ovary, which was removed. The specimen measured 7 by 5.5 by 5 cm., the enlargement being due to replacement of ovarian tissue by follicular cysts. Microscopically, there were multiple follicular cysts and hemorrhagic infarction. The child had an uneventful recovery. In March 1938 she had a pathologic fracture of the right humerus. Repeated roentgen examinations showed progression of the disease of the bones. On May 13, 1939 she became ill with bronchopneumonia, and she died two days later.

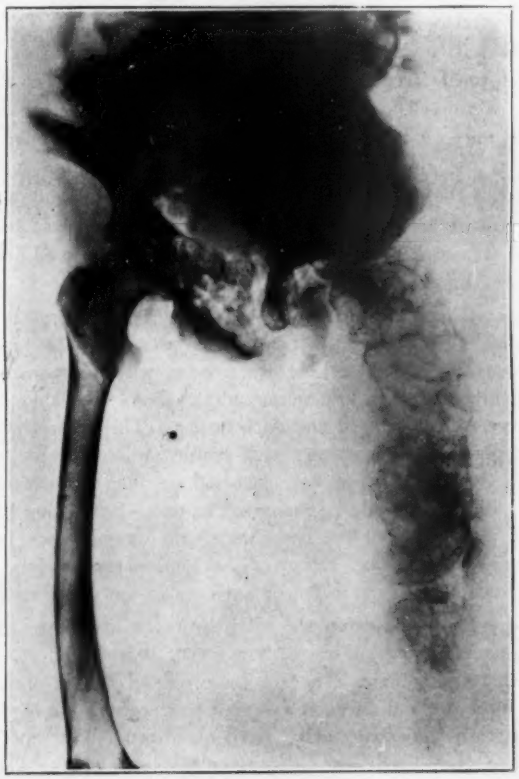

Fig. 5.—The pelvis in 1938 (chronologic age, 12 years). The pelvis is bilaterally involved. The left femur is almost intact compared with the right.

PATHOLOGIC REPORT

The body was that of a misshapen, dwarfed, young white female. The head was large and out of proportion to the size of the body. The face was that of an adult. The skull was irregular and bumpy, the forehead being broad, high and somewhat flattened near the hair line. The temporofrontal areas were prominent. The hair covering the scalp was short, black and moderately fine. The eyes were widely spaced. There was no exophthalmos. The nose was pug shaped, with the bridge flat and broad. The buccal mucosa was free of abnormal pigmentation; the tongue was of average size. All the teeth belonged to the permanent set, but there were marked irregularity and overriding. The cheek bones were prominent

and the lower jaw square but not prognathous. There was an irregular bony mass at the left side of the mandible. The chin rested on the sternum and hid a short neck. There was a well healed operative incision (made for the exploration for parathyroid tumor) at the base of the neck. Small palpable lymph nodes were present on both sides of the neck and also in the axillas and in both inguinal regions.

There was extreme deformity of the trunk, with kyphoscoliosis of the dorsolumbar portion of the spine and torsion of the pelvis with the right side higher than the left. The sternum was displaced anteriorly and elevated at the angle of Louis, where it met the chin. The ribs were irregular, and the lowermost ones flared. There was also extreme deformity of the extremities. The right arm was shorter than the left, owing to shortening of the upper part of the arm. The humerus was deformed, irregular, thickened especially in its upper third and curved out. The hands were well formed. The lower extremities were likewise deformed. They were shortened, with the right much shorter than the left. There were lateral bowing of the right femur and pronounced angulation in the midportion of the lower part of the right leg. The tibia here was large, and on slight pressure its thin rim of cortex was easily broken. There were several operative scars on the extremities. The abdomen was distended. There was a well healed right paramedian scar in the lower part of the abdomen.

Secondary Sex Characteristics.—The development of the breasts was that of an adult, with a moderate amount of firm tissue present. The nipples were well developed and surrounded by deep brown areolas with prominent lacteal glands. The external genitalia were those of an adult. Both the labia majora and the labia minora were well developed and dark brown. The clitoris was adult in type and not hypertrophied. The eyebrows were sparse and black. At the outer corners of the upper lips there were a few fine black hairs. There was a moderate amount of axillary and pubic hair of adult female distribution. Some long hairs surrounded the nipples, and over much of the body there was downy black lanugo-like hair, prominent between the scapulas and over the lumbosacral region, buttocks, right lower extremity posteriorly and extensor surfaces of the upper extremities.

Pigmentation.—The complexion was dark brunette, and there were large areas of dark brown pigmentation of irregular pattern, sharply defined but continuous for the most part over the body. There was an isolated area of pigmentation on the left side of the forehead, and an extensive area was seen on the left side of the face and the neck laterally and posteriorly, extending down on the chest to the region of the xiphoid process. Pigmentation involved the left shoulder and arm and also the interscapular region. Over the lumbar portion of the spine, the sacrum and the buttocks and extending posteriorly down the left leg, there was an even deeper tone of pigmentation. Somewhat lighter patchy areas were present on the remaining portions of the lower extremities. The mons veneris and the axillas were deeply pigmented.

Organs were removed en bloc through an abdominal incision. There were no adhesions or free fluid in the peritoneal or pleural cavities. The serous surfaces were smooth and glistening.

Gross Observations on Organs and Structures (bone and endocrine systems to be considered separately).—Organs of the Neck: The lymphoid tissue of the posterior pharyngeal wall was prominent. The epiglottis and the larynx were not unusual.

Lungs: The appearance was normal except for a large blackish area, soft and moist, at the apex of the lower lobe of the right lung. The hilar nodes were large, soft and pink, as were all the lymphoid structures in the thorax.

Heart: The organ weighed 300 Gm. The measurements of the valve rings were within normal limits. The left ventricular wall was 14 to 18 mm. in thickness; the right ventricular wall, 3 to 5 mm. The foramen ovale was patent for about 5 mm., the opening, however, being completely covered by a fold of endocardium. The heart was otherwise not unusual except for slight hypertrophy and dilatation of the right ventricle and a few soft atheromatous plaques on the aortic leaflet of the mitral valve. The coronary arteries were free of atherosclerosis. The aorta was elastic and contained some areas of lipid deposition and plaque formation at the arch and in the abdominal aorta.

Liver: The organ weighed 850 Gm. and measured 20 by 13 by 6 cm. The shape and size were not unusual. The cut surface was soft and mottled, with irregular, somewhat distorted lobules. A zone of yellow tissue surrounded the central veins in some areas. Other areas were streaked with orange-yellow or brown-red patches. The vessels and ducts were not unusual, but the hilar nodes were large.

Gallbladder and Ducts: These structures were normal.

Spleen: The weight was 190 Gm.; the measurements, 12.5 by 7 by 4 cm. The organ was large, lobulated and firm, with a thin slate gray capsule. On section the cut surface was a dusky purplish red with unusually gray follicles. There were many lymph nodes at the hilus.

Gastrointestinal Tract: Meckel's diverticulum, only 3 cm. in length, was present in the ileum 125 cm. from the ileocecal junction. Peyer's patches were prominent. Prominent lymphoid follicles peppered the distal portion of the ileum and the entire length of the large intestine. The mesenteric lymph nodes were numerous and large.

Genitourinary Tract: Each of the kidneys weighed 120 Gm. and measured 9.5 by 5 by 3 cm. They were of average size, shape and architecture. The bladder, pelves and ureters were normal. The uterus was of average adult size and position. The cervix was long in proportion to the body of the uterus. There was slight congestion at the external cervical os, and the cervical canal was filled with bloody mucoid material. The uterine endometrium was pale pink. The right fallopian tube and ovary were absent (operative removal). The left tube was of adult proportions. The vagina had a pale mucosal surface and prominent rugae.

Microscopic Observations (bone and endocrine organs to be considered separately).—Heart: There was a slight increase in fiber size and nuclear irregularity in both ventricles. The vessels were normal.

Lung: Sections from various lobes of the lungs contained scattered areas with thickening and infiltration of alveolar septums by polymorphonuclear cells and lymphocytes, and capillary congestion. Occasional "heart failure cells" were seen within alveoli. There were areas of emphysema. There was evidence of severe bronchitis with purulent exudate within the lumens of the bronchi, particularly in the lower lobes. A section through the upper portion of the lower lobe of the right lung showed an extensive area of intra-alveolar and intrabronchial hemorrhage, but with intact alveolar walls and no evidence of thrombosis of vessels.

Liver: The hepatic cells contained small vacuoles and granules. Scattered cells, apparently degenerating, contained large acidophilic granules. A small amount

of bile pigment was present in some cells. Small collections of lymphocytes and occasional polymorphonuclear cells were found in the portal areas. Vessels, ducts and fibrous stroma were not unusual. No increase in glycogen content was noted in sections fixed in absolute alcohol and stained by Best's carmine method.

Spleen: The follicles were large and hyperplastic and contained some large cells with large irregular nuclei and blue-staining cytoplasm, occasional polymorphonuclear cells and eosinophils. Many eosinophils were present among the cellular elements of the red pulp. There was great congestion of the red pulp.

Gastrointestinal Tract: In the stomach there was desquamation of the mucosal epithelium. The acinar cells were smaller than normal, suggesting slight atrophy. The mucosa of the jejunum was extremely congested, and there were small areas of hemorrhage. Several collections of fat cells of the fetal type were present in the submucosa and serosa, with liquefaction at the centers of some of these areas. The ileum contained prominent lymphoid follicles. The large intestine and the appendix were normal.

Genitourinary Tract: In the kidneys there was extreme congestion of the vessels. The glomeruli and tubules appeared normal. The bladder showed extensive lymphocytic infiltration of the subepithelial tissue. In several areas the epithelium was altered from transitional type to stratified squamous. The uterus had endometrium of the adult type, but quiescent. The glands were normal, and the myometrium was not unusual. There was some proliferation of the cervical glands, with numerous mucin-containing cysts. Attached to the fimbriated end of the left fallopian tube were several small epithelium-lined cysts containing bluish-staining mucin-like material. The tubal epithelium was normal. The vagina was like that of a normal adult.

Breast: The lobulations appeared normal, but the duct spaces were somewhat distended and contained homogeneous material and some desquamated cells.

Skin (Pigmented Area): The cells of the basal layer of epithelium were loaded with melanin. Pigment was also present in some of the more superficially placed cells and in scattered cells of the corium.

Skeletal Muscle (Extremities): Fat cells appeared between the muscle fibers. Many fibers were fragmented and contained indistinct cross striations.

Gross Examination of Bones.—Calvaria: The bones of the calvaria were greatly thickened and soft. In the frontal and occipital regions the thickness was as much as 2.5 cm. The major portion of the thickening was in the outer table. The bony structure was somewhat porous, but no cysts or areas of cartilage were seen in the sections cut.

Left Femur (Uninvolved): The bone was 27 cm. in length, with pronounced anterior bowing of the shaft. The periosteum was not thickened; the cortex was firm and averaged 4 mm. in thickness. The articular cartilages of the condyles were irregular, with fibrous tags on the surface. On section the architecture appeared normal and the epiphyses were closed. The marrow cavity contained soft, dusky red marrow.

Right Femur: The bone was 18 cm. in length. It was deformed and its contour bore little resemblance to that of a normal femur. The head was broad and flattened, the neck foreshortened and the shaft considerably increased in diameter. Both articular surfaces showed evidence of severe arthritis. The cartilaginous surfaces were scarred, irregular in thickness, dull and discolored. The synovial

membranes were thickened, edematous and congested and formed a prominent pannus at the head. The periosteum was thickened and irregular. The bone was cut sagittally with very little resistance and presented an unusual, variegated pattern. The head, neck and shaft contained large areas of glistening, pearly white islands of cartilage, surrounded by soft bony trabeculae and fibrous tissue. Occupying the upper two thirds of the shaft was a large (4.5 cm.) cavity filled with very soft, dusky red marrow and completely lacking in trabeculae. The lower third of the shaft presented a pattern of irregular areas of cartilage, delicate trabeculae, dusky red

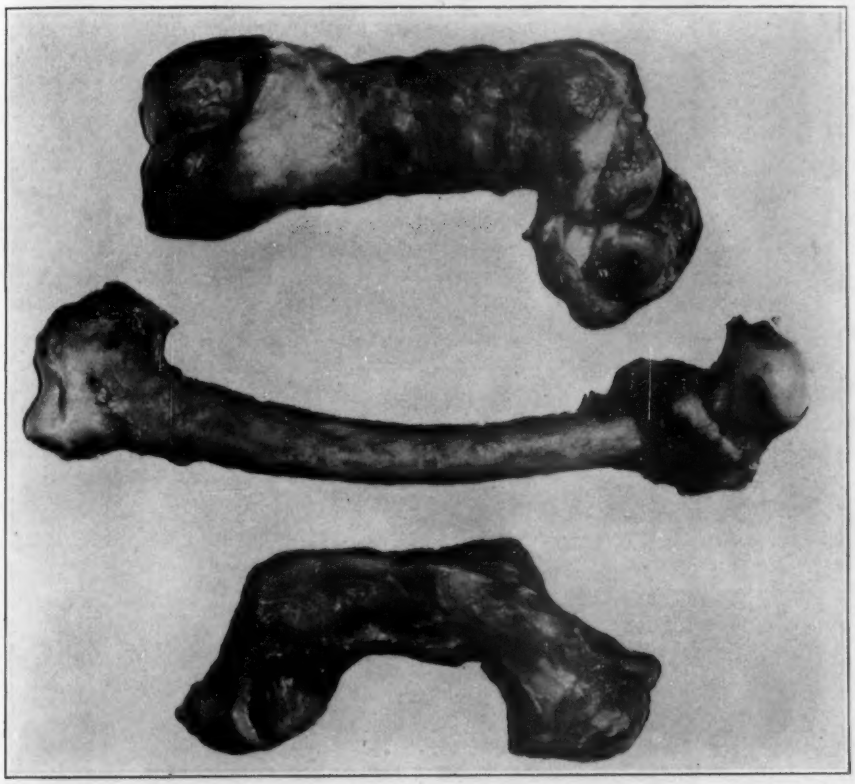

Fig. 6.—The right femur, left femur and right humerus removed at postmortem examination.

marrow and fibrous tissue. The distal epiphysis was similar to the head. The cortex was strikingly reduced and in fact appeared nonexistent in some areas where the marrow cavity was directly contiguous with periosteum. The articular cartilages were represented by no more than a delicate rim of cartilage.

Ilium: A portion of ilium taken out with the right femur and bearing the acetabulum was markedly thickened. The cortex was a thin shell of bone and surrounded a large cavity containing soft, dusky marrow.

Right Humerus: The bone measured 16.5 cm. in length. There were pronounced shortening, thickening and deformity. The bone cut easily. On sagittal section the epiphysis was seen to consist of soft spongy marrow with delicate bony trabeculations. Just below the epiphysial junction in the diaphysis there was a large zone of cartilage traversed by irregular red lines representing bony trabeculae. The main body of the shaft was divided into three large noncommunicating cavities, separated by thin plates of soft bony tissue. The cavities were filled with a sticky yellowish brown fluid. The lining of the cysts was irregular and roughened, with

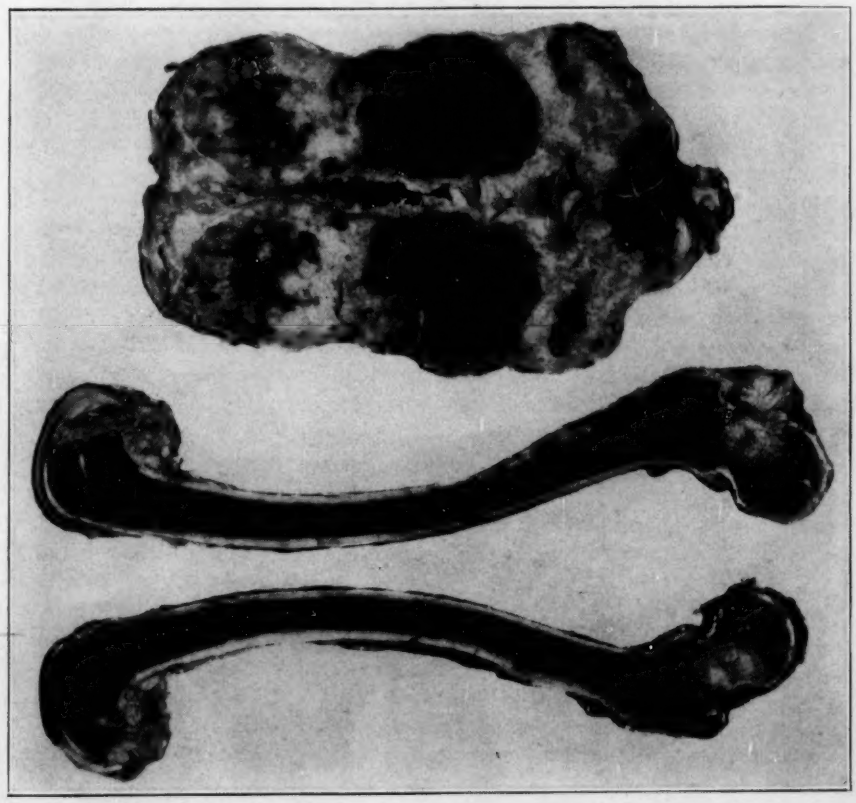

Fig. 7.—The right and left femurs opened longitudinally. In the distorted right femur (upper specimen), the large, dark central area is dense, active marrow free of bony trabeculation. The pale, opalescent areas are islands of cartilage. Note the expansion of the medullary canal and the virtual destruction of cortex. The left femur (lower specimens) is relatively normal (the mottled appearance of the marrow is artefact).

a mottling of pearly gray and hemorrhagic areas. Trabeculae of fibrous tissue (easily broken) traversed the cysts. The upper cavity measured 4.5 cm. in its greatest diameter. The cortex was a thin shell of soft bone covered by an irregular and, in places, enormously thickened periosteum. The distal epiphysis showed

areas of cartilage in the spongy marrow. The articular surfaces showed arthritic changes similar to those in the femurs.

Lumbar Vertebrae: The vertebral bodies were markedly irregular, many wedge shaped. The marrow was firm and dusky red. In the center of the bodies there were small cystic areas filled with soft, untrabeculated marrow and small zones of cartilage. The intervertebral disks were compressed.

Microscopic Examination of Bones.—Head of Right Femur: The joint cartilage was extremely thin and irregular. There was virtually no bony cortex, and in many

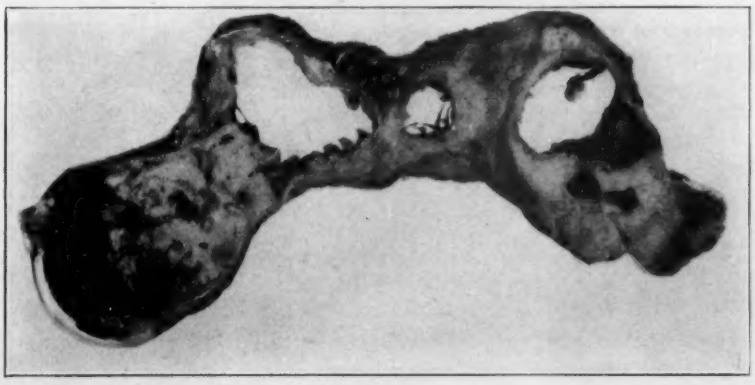

Fig. 8.—A longitudinal section through the right humerus, showing multiple true cysts and islands of cartilage.

Fig. 9.—Section of lumbar vertebrae, showing cystic areas containing active cellular marrow, and islands of cartilage (best seen at right). Note the distortion of the vertebral bodies.

areas the inner aspect of the joint cartilage communicated directly with the marrow spaces of the epiphysis. The usual firm cancellous bone of the epiphysis was replaced by two characteristic tissue patterns: (1) irregular zones of active congested cellular marrow within which were lodged jagged, eroded fragments of bony trabeculae and (2) zones composed of delicate, closely spaced trabeculae the medullary spaces of which were entirely replaced by fibrous tissue. In these fibrous

areas many trabeculae were lined by osteoblasts. Eroded bays and enlarged Howship lacunas within trabeculae were filled with osteoclasts. Dilated thin-walled vascular channels traversed the fibrous tissue. Small areas of hemorrhage, particularly at the junction of marrow and fibrous tissue, were seen, and rare areas of fatty replacement.

Deeper within the head of the femur there were large irregular masses of deep-staining cartilage the cells of which displayed striking variations in size

Fig. 10.—Section through the head of the right femur. In the upper portion is an area of congested cellular marrow containing eroded fragments of bone trabeculae. The lower portion shows an area of delicate, closely spaced young trabeculae, with medullary spaces entirely replaced by loose fibrous tissue.

and arrangement. On the periphery the cartilage was calcified and in many areas undergoing dissolution with simultaneous deposition of osteoid and lamellated bone by osteoblasts. The dissolution of cartilage was accompanied by penetration of vessels into dilated cartilage lacunas and hemorrhage within.

Right Femur Below Greater Trochanter, Adjoining Marrow: The marrow cavity was completely filled by dense, active, hyperemic marrow. The wall of the marrow cavity was lined by collagenous condensation of connective tissue containing zones of blood pigment. The surrounding fibrous tissue varied from the loose embryonal type to the adult collagenous. Occasional cystlike spaces, less than 1 cm. in diameter and filled with active marrow, were entirely similar to the major marrow cavity. The cortex was a thin shell, at times absent, the characteristic replacement fibrous tissue extending directly to the periosteum.

Midshaft of Right Femur: The picture was similar to that of the head of the femur. In addition, there were collections of osteoclasts, frequently associated with hemorrhage, within the connective tissue. In one area there was evidence of transformation of fibroblasts from the inner layer of periosteum into small chondro-

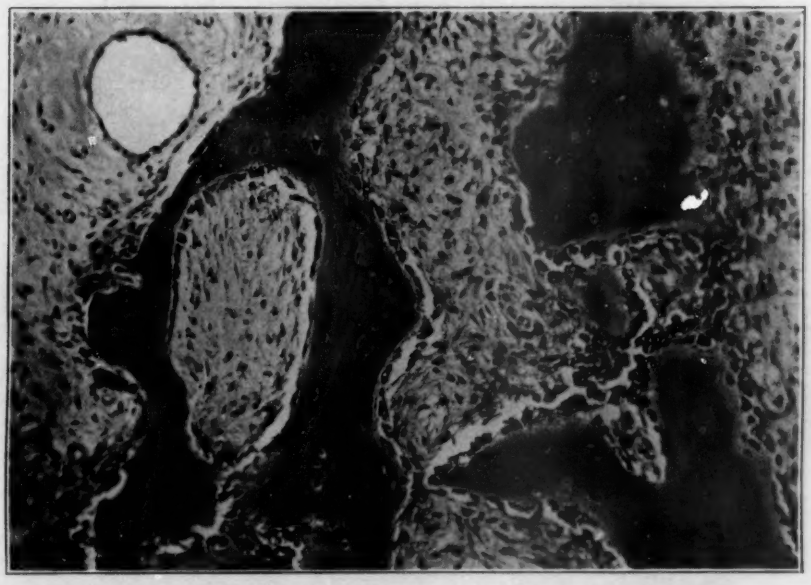

Fig. 11.—Section through the right femur, at the junction of the shaft and the condyle (higher power magnification), showing delicate trabeculae lined with active osteoblasts. The medullary space is replaced by fibrous connective tissue.

blasts and adult cartilage cells, and at the periphery of the latter there were zones of osteoid undergoing calcification. This was an area of old pathologic fracture.

Right Humerus as a Whole: Sections showed changes similar to those in the right femur: osteoclastic resorption, osteoblastic deposition of osteoid and fibrous replacement.

Wall of Cyst in Upper Shaft of Right Humerus: The wall of the cyst was narrow, and the connective tissue lining its inner surface had a loose myxomatous appearance. Except for the ragged edge of fibrous tissue there was no other lining of the cyst cavity. Zones of polymorphonuclear cells, lymphocytes and blood pigment (free and within macrophages) appeared in the connective tissue next to

the myxomatous tissue. Some osteoclasts appeared in the fibrous tissue isolated from bone and often were associated with hemorrhage.

Lower End of Right Humerus with Portion of Cyst Wall: The changes were similar to those just described, with osteoclastic lacunar resorption, osteoblastic repair and fibrous scar formation. Islands of hypertrophic marrow were present, with hemorrhage and osteoclastic resorption more noticeable about these islands. In the fibrous tissue lining the inner surface of the cyst wall there were areas of hemorrhage and numerous osteoclasts lying free or adjacent to bony trabeculae.

Gross and Microscopic Examination of Endocrine Organs.—Thyroid: The gland weighed 16 Gm. and was above average for the size of the body. The shape was usual, but on the lower posterior surface of both lobes there were some tiny adenomas. On

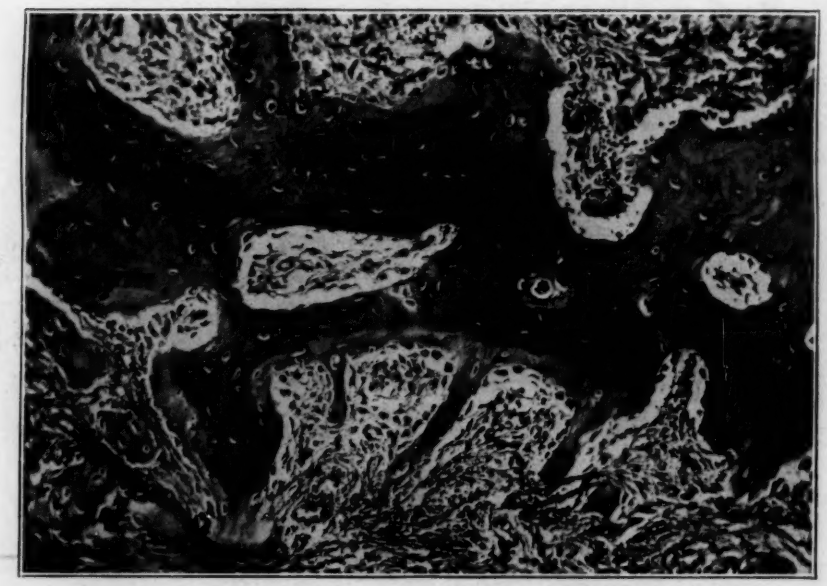

Fig. 12.—Section through the midshaft of the right humerus. Simultaneous deposition and resorption of bone are present. Below, the trabeculae are lined with osteoblasts. Above, there is erosion of the older bone, with numerous osteoclasts within eroded bays.

section the cut surface was amber brown and moderate amounts of colloid were present. There were small adenomatous nodules in the substance of the gland.

Microscopic Picture. There was great irregularity in size and shape of the vesicles, which were lined by columnar or cuboidal epithelium, displaying numerous infoldings. The colloid was pink staining and partly vacuolated. In many vesicles the colloid was separated from the epithelium and the periphery appeared hazy. Numerous small adenomas of the so-called "fetal" type were present, and occasional young adenomas, as yet uncapsulated. There was a moderate increase in interacinar connective tissue and some congestion of vessels, but no lymphocytic infiltration.

Parathyroids: Four glands were found, in the usual positions except that the left lower gland was embedded in the posterior surface of the thyroid. They were all small and pale yellow brown.

Microscopic Picture. The cells were predominantly of the dark chief type, with occasional cells showing clear cytoplasm. Some groups of cells tended to form acini about pink-staining "colloid." There were a slight increase in fibrous

Fig. 13.—Section through the right humerus adjacent to the wall of a cyst. There are extensive erosion of the bony spicules, with numerous osteoclasts, and areas of hemorrhage. Below is the fibrous lining of the cyst wall. The innermost lining is myxomatous in appearance and infiltrated by leukocytes.

tissue, fatty infiltration and moderate congestion. No groups of oxyphilic cells were present. At the numerous levels at which sections were cut through all four glands, only a single microscopic adenoma consisting of water-clear cells was found in one of the parathyroids.

Thymus: The gland weighed 20 Gm. It was a large (particularly in view of the advanced sexual development), soft, lobulated structure with pale pinkish yellow tissue, glandular in consistency.

Microscopic Picture. The gland appeared extremely active, with closely packed lymphocytic cells and many Hassall corpuscles. There was good delineation of cortex and medulla. Very little fibrous stroma separated the individual lobules.

Pancreas: The organ was of the usual size, shape and architecture. The tissues were soft and pinkish, with islands visible in the tail.

Microscopic Picture. The islands were smaller than normal and fewer on the whole. The acinar tissue was normal. The blood vessels, including the capillaries, were congested, and there were a few areas of recent hemorrhage between lobules. In some areas there were an increase in interlobular and interacinar connective

Fig. 14.—Section through the midshaft of the right humerus, showing transformation of periosteal cells to young and finally to adult cartilage cells. The lower left hand portion (*P*) consists mainly of markedly thickened periosteum.

tissue, periductile fibrosis and proliferation of ducts with regeneration of acini in fibrotic areas.

Adrenals: The two glands together weighed 8 Gm. They were small for the body size but of the usual shape and position. On section the cortex was composed of a thin rim of yellow tissue containing a moderate amount of lipid. The pigmented reticular zone was of average size. The medulla was relatively large and translucent gray.

Microscopic Picture. The glomerulosa zone was ill defined and somewhat atrophic. The fascicular zone was narrowed, the cords of cells being of the "lean" variety, in contrast to the prominent dilated sinusoids that traversed this zone. The

pigmented reticular zone was prominent. Staining with ponceaufuchsin after the method of Vines failed to reveal the specific fuchsinophile cells considered by Vines to be androgenic. The medulla was prominent, with plump hyperactive cells which stained deeply with chrome salts on Orth's fixative. In the pericapsular tissue of the right adrenal was an unencapsulated small area of tissue consisting of cells of the pheochrome type.

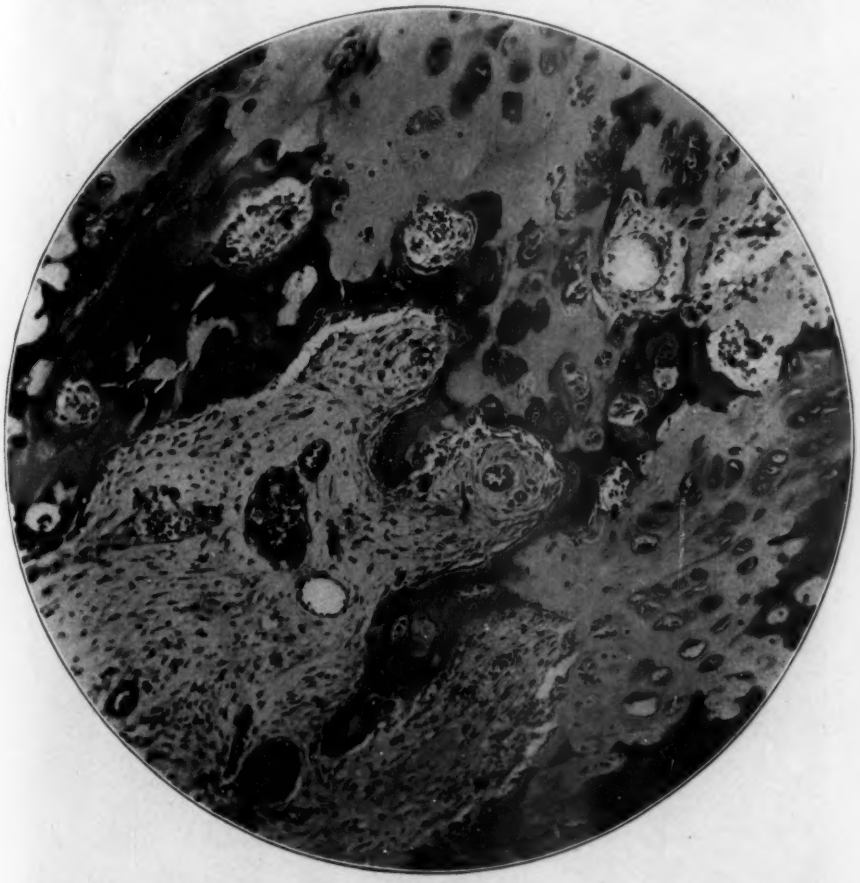

Fig. 15.—Section through the right humerus, at the junction of the shaft and the condyle. There is an irregular mass of cartilage, with striking variation in size and arrangement of cells. Toward the periphery the cartilage is calcified and in some areas undergoing dissolution, with simultaneous deposition of osteoid and lamellated bone at the very periphery. The dissolution of cartilage is accompanied by penetration of vessels into dilated cartilage lacunas and hemorrhage within.

Ovaries: The right ovary was absent (operative removal). The left ovary appeared larger than usual and weighed 4.5 Gm. It was white with a thick capsule, and its surface was scarred. Many small and medium-sized follicular

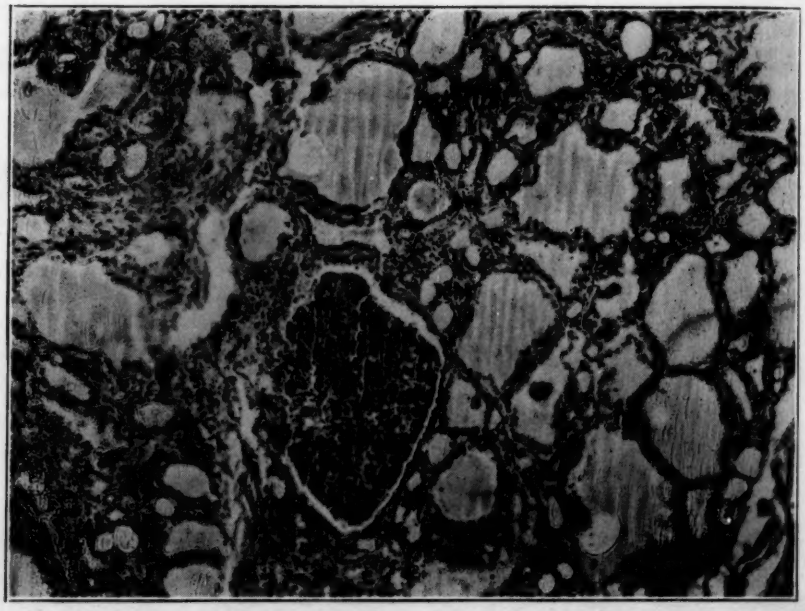

Fig. 16.—Section of the thyroid, showing marked hyperplasia. There is irregularity in size and shape of follicles. The epithelium is cuboidal and columnar, with numerous infoldings. A fetal adenoma is present.

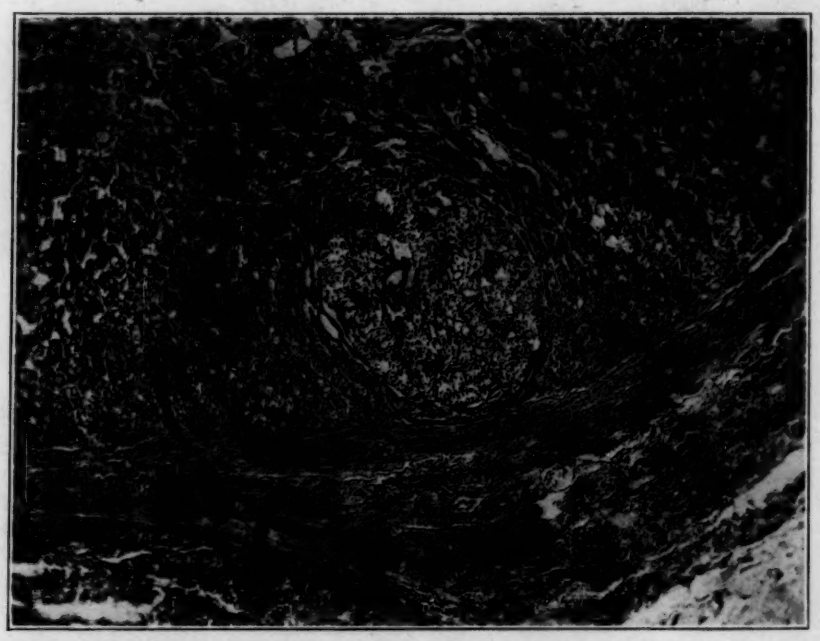

Fig. 17.—Section of a parathyroid. The cells are predominantly of the dark, chief type. The single, minute adenoma of water-clear cells is the only one found, although numerous sections were taken throughout all four glands.

cysts filled with clear fluid were present. There was no evidence of luteinization. Several small parovarian cysts were present, and one larger one, measuring 3 cm. in diameter.

Microscopic Picture. Several large cystlike spaces lined with theca cells, both interna and externa, were present. The walls contained large macrophages filled with brown pigment. There were numerous primordial follicles and some developing follicles, several of which appeared to be undergoing atresia. No definite areas of lutein cells were present; however, there were several areas of scar formation with hemorrhage, phagocytic cells and blood pigment.

(The right ovary, removed surgically seventeen months earlier for acute torsion of the pedicle, revealed a similar picture except for the extensive hemorrhage and necrosis. It was a cystic ovary with a thick capsule and no evidence of luteinization.)

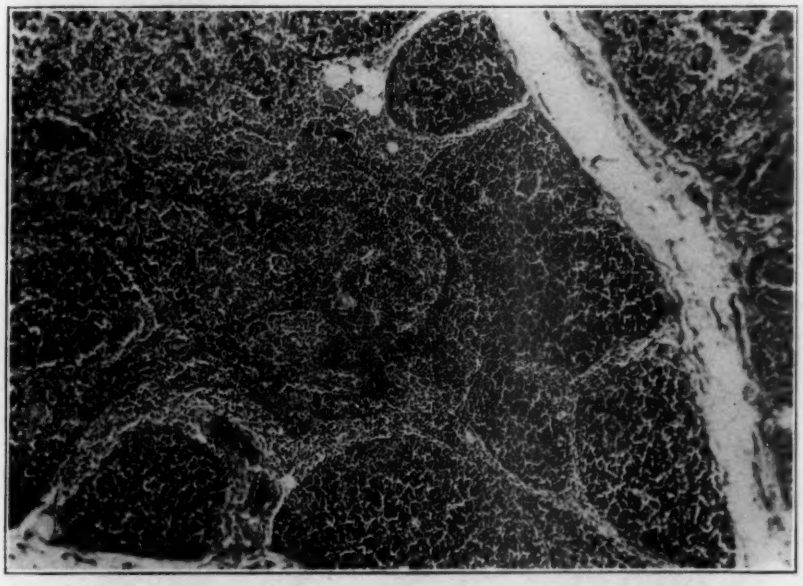

Fig. 18.—Section of the thymus, a large, active, lobulated gland with good delineation of the cortex and the medulla.

Pituitary (Report by Dr. Charles Spark): The gland weighed 530 mg. and measured 16 mm. in transverse diameter, 11 mm. in anteroposterior diameter and 6 mm. in vertical diameter. This was considered large for the body weight and the chronologic age, although part of the increased weight was undoubtedly due to congestion. On gross section the anterior lobe was deeply congested and contained many small opaque, grayish areas (adenomatoid nodules).

Microscopic Picture. There was intense engorgement of the capillaries, with many foci of rupture and extravasation of blood between cell columns. Edema was present in some areas. There were extreme pleomorphism, especially of the basophilic elements, and distortion of the architecture. A striking increase in the basophils at the expense of chromophobe cells was apparent. It is estimated that the basophils comprise 40 to 50 per cent of the cells of the anterior lobe and the

chromophobe cells 5 to 10 per cent, a reversal of the usual percentages. Further evidence of the basophilic hyperplasia was expressed in the pronounced tendency to basophile adenoma formation revealed in all seven levels studied. This was present throughout the inferior half of the anterior lobe.

The basophils in general were larger than those of normal pituitaries of a comparable age (12 years). The cell size, as indicated by camera lucida drawings,

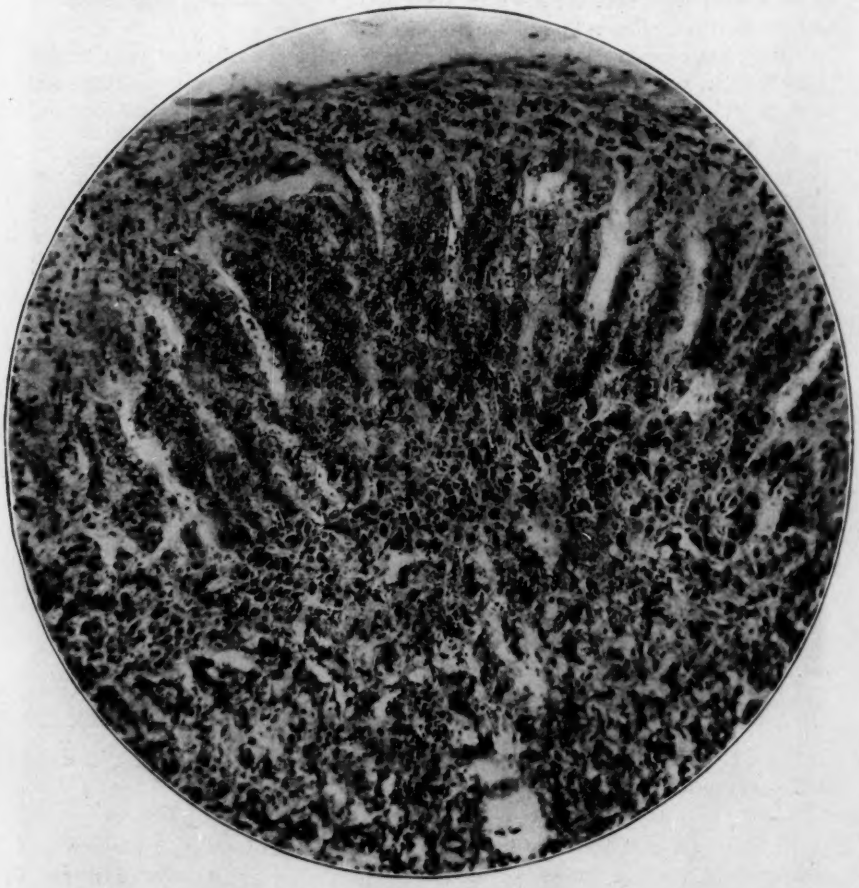

Fig. 19.—Section of an adrenal gland. The glomerulosa zone is ill defined and somewhat atrophic. The fascicular zone is narrowed, the cells "lean" in type and the sinusoids dilated. The pigmented reticular zone is prominent. The medulla (lower part of section) is large and the cells plump.

was about that of an adult, and the nuclear size was even larger than that of normal adults. This increase in the nucleus to cytoplasm ratio, as well as the marked pleomorphism, the vesicular character of the nuclei, the diminished chromatin content and the large numbers of binucleated and trinucleated cells, was suggestive of cells whose function had been disturbed. The majority of basophils showed

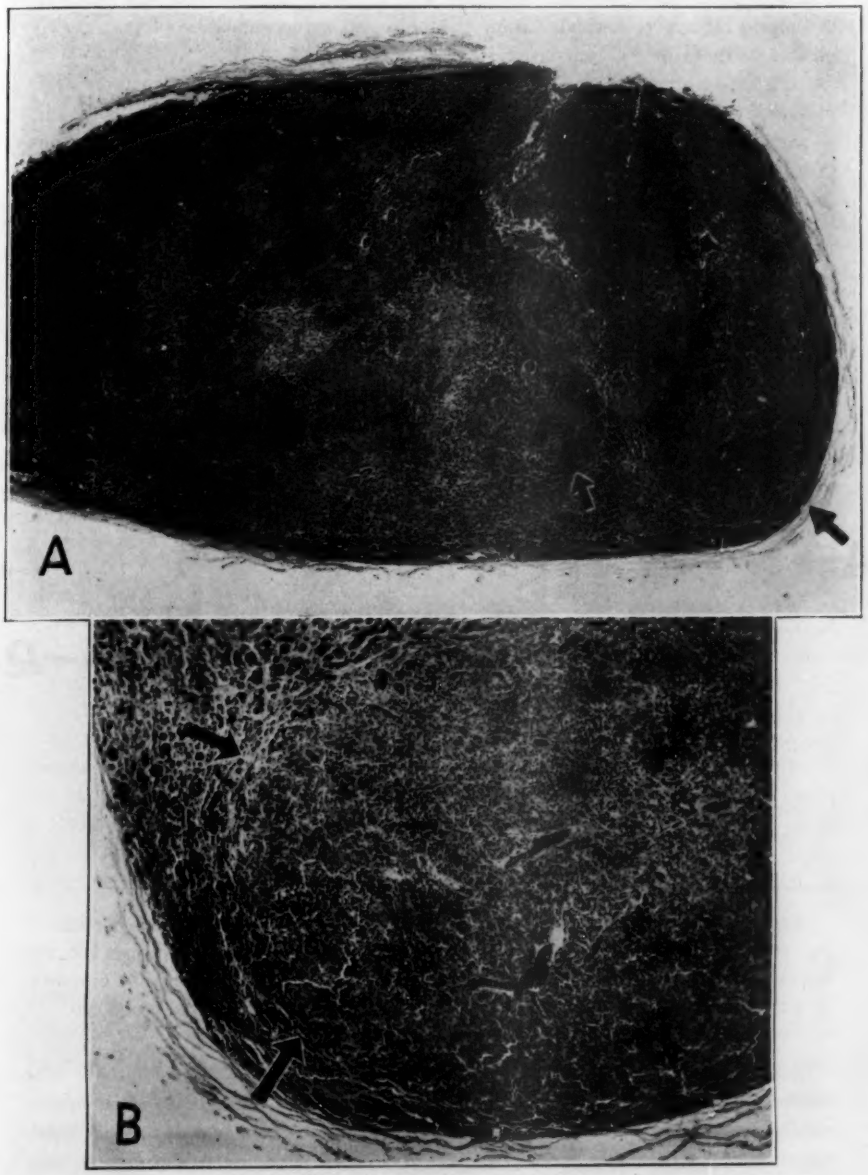

Fig. 20.—*A*, sagittal section of the anterior lobe of the pituitary, showing circumscribed nodules (indicated by arrows) of basophilic cells. *B*, higher power magnification, showing a circumscribed nodule of basophilic cells.

granule loss with colloid cytoplasm, many closely resembling the typical Crooke colloid basophil. There were relatively few basophils, isolated or in follicles, which retained their dustlike granules, and in these the cell size and nucleus-cytoplasm ratio were normal. Many basophils had an accumulation of fine, closely packed vacuoles in the cytoplasm.

The acidophils were small and showed much less variation in structure. The majority were definitely smaller than those of normal pituitaries of the same age, as shown by camera lucida tracings. Occasional acidophils within the adenomatous areas were larger than normal.

Rathke's cleft was intact. The posterior lobe showed no changes except congestion. There was no basophilic invasion of the posterior lobe.

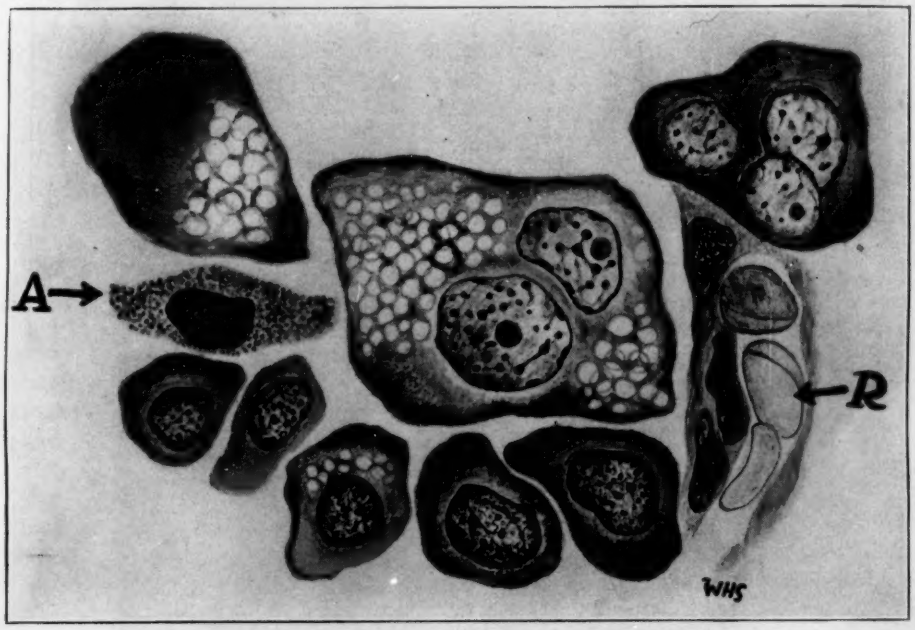

Fig. 21.—High magnification drawing of cells in the adenomatous portion of the anterior lobe of the pituitary, showing the striking pleomorphism of the basophilic cells, with their vesicular, often multiple, nuclei and fine, ductlike granules. *A* is an acidophil. A sinusoid is present on the right side. *R* is a red blood cell.

Interpretation of Histologic Observations on Endocrine Glands.—Thyroid: The histologic picture was typical of hyperplasia. In addition, there were numerous small adenomas of the "fetal" type. The presence of adenomas is usually associated with long-standing overactivity of the gland with alternating hypertrophy and partial regression. This results in an uneven blood supply which causes groups of cells that stand in a better relation to the blood supply to grow more rapidly. The presence of numerous adenomas, then, suggests that the hyperplasia was not of recent origin but of long standing, which is consistent with the long clinical history of exophthalmic goiter.

Parathyroids: The histologic appearance was within normal limits, only occasional water-clear cells being present. The absence of any clumps of oxyphile cells (generally considered as spent or inactive cells) might suggest some activity, but the patient was only 12 years old and oxyphile cells do not usually appear until well over the age of 10 years.

Thymus: The enlargement of the thymus, as well as other lymphoid structures, was striking. The thymus appeared as an active glandular structure with very little stroma. Experimentally, such thymic and lymphoid hyperplasia is most readily initiated by either increased thyroid activity or adrenal cortex insufficiency. This is of interest in view of the presence of exophthalmic goiter.

Adrenals: The narrow cortex with small, lean cells, despite the prominent blood sinusoids, was suggestive of tissue subjected to increased demands but nevertheless losing ground. The medulla presented a picture of hyperactivity.

Ovaries: The ovary was mature, with numerous primordial and developing follicles and follicular cysts. The absence of luteinization, the thick capsule and the areas of scar formation, with hemorrhage, phagocytic cells and blood pigment, suggested failure of follicle rupture through the capsule. Instead, there was hemorrhage into graaffian follicles with lack of development of lutein tissue or its early destruction by pressure necrosis.

Pituitary: The most important change was a hyperplasia of the basophilic elements, with remarkable pleomorphism, and a tendency to adenoma formation. The large majority of basophils showed loss of granules. The picture was that of a gland showing evidence of prolonged stimulation and activity, especially of the basophils. There was, however, no suggestion of a primary pituitary disturbance which could be considered of etiologic significance.

Neuropathologic Report.—The brain was examined by Dr. Charles Davison. It weighed 1,300 Gm., and the convolutional markings were normal. Coronal sections failed to reveal any pathologic changes. The ventricles were normal, with the possible exception of the third, which was considered very slightly dilated. Sections were taken through the parietal convolutions, third ventricle and medulla oblongata and were stained by the myelin sheath and cresyl violet methods. All of the sections studied, including numerous sections through the hypothalamus, were considered within normal limits. There was no neuropathologic diagnosis.

COMMENT

BONE

1. General Pathology.—The fundamental pathologic processes in the bones in this case consisted of a severe degree of bony destruction by osteoclastic lacunar resorption and a heroic but inadequate attempt at repair. The bony destruction produced softening, distortion, fibrous replacement and cyst formation. The trabeculae of the spongiosa were narrowed by resorption, invaded and surrounded by zones of connective tissue. The vessel canals were enlarged and filled with connective tissue. Osteoclasts and Howship lacunas were a prominent accompaniment of the process of resorption.

Where the process was of long standing, little was left of the original osseous tissue and the entire architecture of the bone was grossly distorted. Large tracts of connective tissue, replacing the original

spongiosa, surrounded fragmented trabeculae of old bone and delicate, poorly calcified trabeculae of newly formed bone. The cortex was invaded by fibrous tissue, narrowed and in places virtually nonexistent. Pathologic fractures with necrosis, hemorrhage and callus formation further complicated the picture. Cysts probably formed as the result of ischemia and hemorrhage associated with bony resorption, and subsequent liquefaction necrosis.

The attempts at repair were an integral part of the pathologic picture. The extensive fibrosis noted was, in effect, scar formation. Bony replacement within the connective tissue was osteoblastic. The presence of cartilage in irregular islands throughout many of the involved bones was striking. We consider this a supreme attempt by the organism at healing by chondrification and subsequent ossification. In this sense there was nothing specific in the process. The irregular islands of cartilage throughout were invariably the site of endochondral ossification at their periphery. There were preliminary calcification of the cartilage, vascular invasion and dissolution, and osteoblastic deposition of bone on the remaining islands. The cartilage was an intrinsic phase in the process of repair by endochondral ossification. It is unnecessary to assume the existence of cartilage rests deep within the shaft, for it is known that the young connective tissue of bone has the potentiality of forming cartilage and that even in adults the healing of fractures sometimes occurs by preliminary deposition of cartilage. The picture is unrelated to enchondromatosis, which furthermore does not involve the membranous bones, although they are severely involved in this syndrome.

Bone, an extremely labile tissue, has nevertheless but limited modes of histologic response to stimuli acting on it. Absorption, growth and repair occur by a limited number of histologic processes. There is, therefore, nothing specific about the histologic appearance of bone in a variety of pathologic and physiologic states. Variations occur in the general pattern of these few modes of response (such as the "mosaic pattern" of Paget's disease) and in the general tempo of activity.

It is not surprising, then, that this picture should in many respects simulate von Recklinghausen's disease, although clearly there is no evidence of a parathyroid origin. In both, there are severe bone absorption and attempts at repair. Cyst formation occurs in both. The syndrome under consideration differs somewhat in the fewer number of osteoclasts than is generally seen in von Recklinghausen's disease, the age distribution (von Recklinghausen's disease is rare in the young), and the absence of clasmatocytomas, or brown tumors. This may merely be a manifestation of a somewhat slower tempo of the disease process. The presence of cartilage, as already noted, is not regarded as specific, and its absence generally in von Recklinghausen's disease may be an expression of a later age distribution.

Lichtenstein [8] has described a group of diseases of bone which he terms polyostotic fibrous dysplasia, and he has expressed the opinion that the condition observed in the cases of Albright [1] and his co-workers, as well as that in the present case (as reported by McCune and Bruch [2]), belongs to this group. Roentgenographically the manifestations are similar, and in both syndromes the lesions are often predominantly unilateral. However, in the cases of Lichtenstein there was no pigmentation, precocious puberty or other endocrine disturbance and, further, the onset of symptoms occurred at a somewhat later age. The essential lesion in Lichtenstein's cases was the filling in of the marrow cavity by fibrous tissue, within which poorly formed bony trabeculae and areas of cartilage developed by osseous and cartilaginous metaplasia of the fibers. He expressed the belief that there was no true cyst formation, although his material was derived from isolated biopsies of bones. In our case there was definite cyst formation and the bone repair was osteoblastic in type, with areas of bone formation from cartilage comparable to endochondral ossification. The two pictures, we believe, are distinct.

The possibility of the lesions in the bones being produced by xanthomatosis or any other lipid storage disease, as suggested by some authors, is eliminated by the histologic evidence.

Braid,[4] in her report of 2 cases of this syndrome, has developed the hypothesis of damage of the liver as the etiologic factor. In several cases, including the one reported here, there has been a history of neonatal icterus, but such a finding, because of its frequency generally, is rather difficult to evaluate. That the disease is not produced by damage to osteogenetic cells, the result of jaundice, is attested to by the evidence of active osteoblastic repair in the diseased bones. It is not due to failure of storage of vitamin D in the liver, for the histologic appearance of the bones bears no resemblance to that in rickets. The presence of neonatal jaundice in some of these cases may be an unexplained manifestation of the disease. We do not believe, however, that it is of etiologic significance.

2. The Problem of Asymmetry.—The existence of predominantly unilateral lesions of bones in many cases of this syndrome has led to some speculation as to causation. The possible relation to lesions of the nervous system and to developmental defect has been discussed by many authors. Albright, for example, has concluded that since the lesions have a unilateral character they cannot be primarily endocrine or metabolic in origin. However, it is difficult to comprehend how a disease of bone which is characterized by an increased rate of

8. Lichtenstein, L.: Polyostotic Fibrous Dysplasia, Arch. Surg. **36**:874-898 (May) 1938.

bone absorption and repair, and which is progressive (involving bone which previously was roentgenologically normal) can be other than metabolic. Developmental defect alone cannot explain such a dynamic sequence of events.

The action of endocrine factors, since they exercise their effects through the blood stream, is of course characteristically diffuse. However, the action of a hormone is determined not alone by its existence within the blood stream but also by local tissue susceptibility to response. Examples may be cited from other endocrine syndromes. Exophthalmos in exophthalmic goiter is occasionally unilateral, and usually asymmetric. In experimentally produced exophthalmos in animals, often one side is markedly more exophthalmic than the other.[9] A few rare cases of predominantly unilateral acromegaly, hemihypertrophy and hemiobesity have also been reported, as well as unilateral gynecomastia with cortical adrenal and testicular tumors.[10] In these instances the endocrine stimuli undoubtedly are diffuse and the unilateral response must be interpreted as due to alterations in local tissue reaction to the humeral stimuli. More specifically, in renal rickets the changes in the bones, as Teall [11] has pointed out, are often patchy and asymmetric. In von Recklinghausen's disease of parathyroid origin, the response in the bones is usually universal, although here again occasional asymmetric variations occur. In that disease, moreover, osteoporosis is generalized, in contrast to the syndrome under discussion, in which there are striking discrepancies in osseous response, for example, the almost normal femur on the left contrasted with the deformed, diseased femur on the right.

The reasons for the variation in local tissue response are of course obscure. Neural stimuli, autonomic or otherwise, may play a role. In the present case there were no neuropathologic observations of significance, although the limitation of our technics of pathologic investigation must be recognized. Furthermore, there is little experimental evidence to indicate any trophic influence on development of bone. It has long been known that complete sympathectomy has no effect on growth and development of bone (Cannon and his group). Numerous experiments on spinal nerve section have shown no effect on bone other than the atrophy of disuse subsequent to concomitant paralysis of muscle. Corbin and Hinsey,[12] working with sympathectomized, deaf-

9. Marine, D.: Does the Study of Experimental Exophthalmos Offer Any Clue to the Fundamental Nature of Graves' Disease? Tr. Third Internat. Goiter Conf. & Am. A. Study Goiter, 1938, pp. 7-16.

10. Weber, F. P.: Asymmetry or "Unilateralism" in "General" Disturbances of Growth, M. Press **175**:244 (Sept. 21) 1927.

11. Teall, C. G.: Radiological Appearances of Certain Bone Dyscrasias in Infancy and Childhood, Proc. Roy. Soc. Med. **27**:1385-1393 (Aug.) 1934.

12. Corbin, K. B., and Hinsey, J. C.: Influence of Nervous System on Bone and Joints, Anat. Rec. **75**:307-317 (Nov. 25) 1939.

ferented preparations, concluded that no trophic effects could be demonstrated.

Developmental factors may be considered, although here again one is in the realm of speculation. It is conceivable that a defective anlage may in some way alter local tissue susceptibility to subsequent hormonal stimuli acting over a long period. It must be recognized, too, that such developmental anomalies may themselves be the result of endocrine stimuli acting during intrauterine life, for example, the production of permanent hermaphroditism in the offspring by giving the gestating mother animal injections of androgenic or estrogenic substances (Greene, Burrill and Ivy [13]). The existence of Meckel's diverticulum and the patency of the foramen ovale in our case may lend some credence to this possibility, since it is known that developmental defects often are multiple.

Finally, voluntary movement and sparing of certain extremities may contribute to the asymmetry. Development of pathologic fractures and subsequent atrophy of disuse may exaggerate the asymmetry of the lesions. It is noteworthy that the skull and vertebrae in this case were bilaterally involved. In several reported cases the lesions were distributed bilaterally.

3. The Endocrine Factors.—Roentgenologic as well as pathologic evidence revealed a strikingly advanced bone age, with premature closure of the epiphyses and consequent dwarfism. Such conditions have been frequently observed in other cases of precocious puberty, although the endocrine factors involved are poorly understood. Several factors may be involved. Precocious increase in estrogens may itself affect development of bone directly or indirectly. Estrogen injected into infantile guinea pigs resulted in premature calcification of long bones and consequent stunting, according to Seemann.[14] Talbot [15] reported significant precocious advances in the skeletal age after administration of estradiol in immature female rats but not in males. M. and R. Silberberg [16] showed increased hyalinization and ossification of intercartilaginous ground substance in epiphysial disks, ribs and vertebrae of immature guinea pigs following estrogens. Accelerated and widespread absorption

13. Greene, R. R.; Burrill, M. W., and Ivy, A. C.: The Experimental Production of Intersexuality in the Female Rat, Am. J. Obst. & Gynec. **36**:1038-1046 (Dec.) 1938.

14. Seemann, H.: Ueber das Vorkommen des Östrins in den Hoden und seine Wirkung auf das Knochenwachstum, Endokrinologie **18**:225-234, 1937.

15. Talbot, N. B.: Effect of Estrogen on Skeletal Age of Immature Rats, Endocrinology **25**:601-604 (Oct.) 1939.

16. Silberberg, M., and Silberberg, R.: Action of Estrogen on Skeletal Tissue of Immature Guinea-Pigs, Arch. Path. **28**:340-360 (Sept.) 1939.

in the cortex and trabeculae of bone was found.[17] Comparably, testosterone in prepuberal rats produced an initial increase in growth of the head of the tibia but subsequent accelerated ossification, so that the total bone length was less than that in controls (Sainton, Simonnet and Petrescu [18]). The thyroid has been known to accelerate skeletal age and produce premature closure of the epiphyses, both experimentally with thyroid feeding [19] and clinically in cases of exophthalmic goiter.[20] Conversely, myxedematous states are associated with retardation of bone development. These findings are of interest in view of the existence of exophthalmic goiter in this case in association with gonadal disturbance.

These interrelationships, furthermore, may furnish a clue to the specific pathologic condition of the bone characterized by bony resorption and cyst formation, with attempts at repair. The increased excretion of calcium and phosphorus in exophthalmic goiter, with normal blood values and normal parathyroid (as are also present in this case), has been elucidated by Aub and his co-workers.[21] Osteoporosis clinically is not uncommon in exophthalmic goiter. Occasionally, in prolonged states, it may lead to pathologic fractures, and rarely to cyst formation. The process, as Askanazy and Rutishauser,[22] Martos [23] and others have

17. The relation of bone disease to gonadal disturbance in this syndrome finds further support in the recent experimental work of J. L. Bremer (Osteitis Fibrosa Localisata, Arch. Path. **32**:200-210 [Aug.] 1941). Bremer pointed out that the pneumatization of long bones in growing birds (a process, incidentally, which resembles closely the histologic changes in osteitis fibrosa cystica) is probably due to the high content of estrogens in the yolk sac. Young white rats were treated with estrogens and similar changes noted. Osteoblasts from the inner layer of periosteum underwent dedifferentiation to a mesenchymatous tissue which, extending inward, eroded spicules of bone and produced an osteoclastic reaction. In the bones of rats, after cessation of estrogen treatment localized areas of mesenchymal fibrous tissue were found which in some cases had undergone differentiation to cartilage. In short, *localized* lesions histologically characterized by fibrosis, bone erosion, osteoclast production and cartilage formation have been produced by endocrine stimuli. The relationship to the syndrome under discussion is apparent.

18. Sainton, P.; Simonnet, H., and Petrescu, J.: Influence de l'hormone mâle sur le développement du rat mâle impubère, Compt. rend. Soc. de biol. **128**:698-700, 1938.

19. Smith, E., and McLean, F.: Effect of Hyperthyroidism upon Growth and Chemical Composition of Bone, Endocrinology **23**:546-552 (Nov.) 1938.

20. Coryn, G.: Les affections endocriniennes du squelette, Presse méd. **46**:228-231 (Feb. 12) 1938.

21. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: Studies of Calcium and Phosphorus Metabolism: Effects of Thyroid Hormone and Thyroid Disease, J. Clin. Investigation **7**:97-137 (April) 1929.

22. Askanazy, M., and Rutishauser, E.: Die Knochen der Basedow-Kranken. Beitrag zur latenten Osteodystrophia fibrosa, Virchows Arch. f. path. Anat. **291**: 653-681, 1933.

23. Martos, J.: Knochenveränderungen bei experimentellem Hyperthyreoidismus und bei Basedow-Krankheit, Beitr. z. path. Anat. u. z. allg. Path. **100**:293-308, 1938.

shown, is characterized by osteoclastic lacunar absorption. It is conceivable that similar factors may operate in the case under discussion, though clearly the situation is much more complex. The absence of generalized osteoporosis and the patchiness in distribution of lesions predicate, as has been suggested, some alteration in local tissue response of which little is known.

PRECOCIOUS PUBERTY

The phenomenon of precocious puberty may, for purposes of discussion, be divided into two broad types. In the one, essentially an artificial precocious puberty, the normal mechanism of activation of the gonads via the pituitary never occurs. Instead, tumor formation in structures capable of elaborating estrogen or androgen, for instance the adrenal cortex or the gonads, initiates the development of secondary sex characteristics by prematurely supplying the hormone in high concentrations. Characteristically, the gonads themselves do not mature and, if anything, are atrophic, inasmuch as the prolonged high level of androgen or estrogen inhibits the production of pituitary gonadotropin. A review of a large series of cases of precocious puberty associated with adrenocortical tumors and gonadal tumors confirms the presence of immature or atrophic gonads. The situation is exactly comparable to the prolonged injection of androgen or estrogen into immature animals, with development of secondary sex characteristics but atrophy of the gonads. The second type, or true precocious puberty, is characterized by normal but premature activation of the gonads via the pituitary. The gonads precociously mature and elaborate sex hormones. The reasons for this premature activation are obscure. There is no evidence that a primary pathologic condition in the anterior lobe of the pituitary gland initiates precocious puberty. In many cases precocious puberty is associated with an intracranial lesion involving or producing pressure on the hypothalamus, such as a pinealoma or a tumor of the third ventricle. It is of interest that pinealomas associated with precocious puberty have with a single exception been found only in males, whereas in the syndrome under consideration here precocious puberty occurs only in females. Inflammatory involvement of the hypothalamus may also be associated with precocious puberty.[24] In still other cases no obvious underlying pathologic condition is discernible. The precocious puberty in the syndrome under discussion is clearly of this type. The ovaries are mature; no tumor of the adrenal cortex or ovaries is present. Neuropathologic examination reveals no significant lesion. The mechanisms which may

24. Ford, F. R., and Guild, H.: Precocious Puberty Following Measles Encephalitis and Epidemic Encephalitis with a Discussion of the Relation of Intracranial Tumors and Inflammatory Processes to the Syndrome of Macrogenitosomia Praecox, Bull. Johns Hopkins Hosp. **60**:192-203 (March) 1937.

initiate this train of events are probably multiple. Several are mentioned in the discussion under exophthalmic goiter. The exact mechanism of activation of sexual maturity in this syndrome remains a matter of speculation.

EXOPHTHALMIC GOITER

The occurrence of exophthalmic goiter in this syndrome, of which perhaps only 26 probable cases are reported in the literature, is significant enough to be considered other than coincidental. In the present case, in addition to the clearcut clinical findings, the pathologic observation of enlargement and hyperplasia of the thyroid and hyperplasia of the thymus and lymphoid structures confirms the existence of severe exophthalmic goiter. Another case of frank exophthalmic goiter was found in the literature, that of H. H. Musser and R. Barnwell, reported in the discussion following the paper of Albright, Scoville and Sulkovitch.[1b] The findings in this case of an 11 year old boy with osseous disease and pigmentation but without precocious puberty included basal metabolic rates of + 40 and + 60, a pulse rate of 128, a blood pressure of 154 systolic and 70 diastolic and a blood cholesterol content of 78 mg. per hundred cubic centimeters. A subtotal thyroidectomy was performed, but the patient died postoperatively. In the 2 cases reported by Summerfeldt and Brown,[7] the authors commented on the elevated basal metabolic rates, although definite clinical evidence of exophthalmic goiter was lacking. In 1 case a large thymus (for which the child received roentgen therapy) was present; the pulse rate was 90 to 108 and the blood pressure 120 systolic and 84 diastolic; basal metabolic rates of + 10 and + 14 per cent were obtained. In the other case the blood pressure was 140 systolic and 75 diastolic and the basal metabolic rates were + 27 and + 22 per cent. In Gaupp's [25] case the patient had bilateral exophthalmos and a moderate-sized thyroid. In Goldhamer's [26] case there was "slight exophthalmos bilateral but asymmetric," although the thyroid was not enlarged. Exophthalmic goiter could conceivably have existed at one time or another in some of the other cases in which clinical reports and histories were incomplete, and, furthermore, the atypical manifestations might readily have been overlooked in some. At any rate, symptoms of exophthalmic goiter have been observed in a sufficient percentage of the reported cases to be suggestive.

The existence of exophthalmic goiter in the puzzling case reported here may furnish a valuable clue to the fundamental pattern of endocrine imbalance underlying the syndrome. It is apparent, of course, that the

25. Gaupp, V.: Pubertas praecox bei Osteodystrophia fibrosa, Monatschr. f. Kinderh. **53**:312-322, 1932.

26. Goldhamer, K.: Osteodystrophia fibrosa unilateralis (kombiniert mit Pubertas praecox und mit gleichseitigen osteosklerotischen Veränderungen des Schädels), Fortschr. a. d. Geb. d. Röntgenstrahlen **49**:456-481 (May) 1934.

endocrine disturbance here is even more complex than that of exophthalmic goiter, and it would be foolhardy to attempt to explain the protean manifestations of this syndrome entirely in such terms. Nevertheless, a common background probably exists. Certain relationships are thought provoking. Osseous disease characterized by lacunar osteoclastic absorption, normal parathyroids and normal blood calcium and phosphorus values (as in this syndrome) may in the presence of exophthalmic goiter progress to the extent of pathologic fractures and, rarely, cyst formation. Exophthalmic goiter in children is known to be associated with premature osseous development, such as exists in this syndrome. Experimentally, feeding of thyroid to rats results in premature growth of bone and early closure of the epiphyses. Exophthalmic goiter is not infrequently associated with cutaneous melanotic pigmentation. Gudernatch [27] has shown precocious metamorphosis of tadpoles that were fed thyroid.

The broad conception of exophthalmic goiter as involving a profound disturbance in the adrenal cortex and gonads with compensatory (although often harmful) activity of the thyroid gland has been developed by Marine [28] on experimental and clinical evidence. The fundamental disturbance of ovarian and possibly adrenal factors in the syndrome under discussion may bear a similar relation to the thyroid. The ovaries in the case reported were mature cystic ovaries with many developing graafian follicles but no evidence of luteinization. The adrenals were small (together weighing 8 Gm.), even considering the small size of the body. The cortices were narrowed, with atrophic glomerular and fascicular zones, while the medullae were well developed. (A small adrenal with a well developed medulla is a frequent finding in exophthalmic goiter.)

Marine and Baumann [29] have shown that a sublethal injury to the adrenals in rabbits and cats produces a transient picture closely simulating exophthalmic goiter. The outstanding symptoms are increased metabolism, myasthenia, regeneration of the thyroid and hypertrophy of the lymphoid structures, increased appetite, increased irritability and susceptibility to drugs. A comparable situation, as Marine and his co-workers have shown, exists in the human infant. The adrenal cortex in the latter part of intrauterine life and in the period immediately after birth is unusually large. Involution of this hypertrophic cortex begins

27. Gudernatch, J. F.: Feeding Experiments on Tadpoles: II. A Further Contribution to the Knowledge of Organs with Internal Secretion, Am. J. Anat. **15**:431-480, 1914.

28. Marine, D.: Remarks on the Pathogenesis of Graves' Disease, Am. J. M. Sc. **180**:767-772 (Dec.) 1930.

29. Marine, D., and Baumann, E. J.: Influence of Glands with Internal Secretion on Respiratory Exchange: II. Effect of Suprarenal Insufficiency (by Removal or by Freezing) in Rabbits, Am. J. Physiol. **57**:135-152 (Aug.) 1921.

about the eighth day after birth and results in a striking decrease in the size of the cortex during four weeks. Coincidentally with the rapid involution of the adrenal cortex there is a rapid rise in heat production.[30] Marine and his co-workers have interpreted the hypertrophy of the adrenal cortex in intrauterine life as a factor controlling or inhibiting the rate of tissue oxidation in the rapidly growing fetus. From the study of the cases under discussion in this paper, it is apparent that the metabolic or endocrine disturbance that exists must be initiated early in infancy or even in intrauterine life. Conceivably, a disturbance of this adrenal-thyroid mechanism (possibly a premature involution or lack of development of the fetal adrenal cortex) might have been a factor in initiating the hormonal imbalance in these cases. Exophthalmic goiter may be one aspect of this imbalance.

Further, adrenalectomy in rabbits is known to produce a marked hypertrophy of the interstitial cells of the ovary but has no apparent effect on the testis.[31] This mechanism initiated by adrenocortical insufficiency and probably acting through the pituitary might set off the development of precocious puberty through its effect on the ovary. It is of interest that in most of the numerous cases of this syndrome reported the patients have been females and the condition has been associated with precocious puberty, whereas none of the afflicted males have had precocious puberty.

In summary then, there are numerous suggestive interrelationships in the pattern of endocrine disturbance in this case. Some degree of adrenocortical insufficiency may, on the one hand, be related to the initiation of exophthalmic goiter; on the other, of precocious puberty. The disease of the bones bears certain resemblances to the osseous disturbance of exophthalmic goiter, although here again the picture is far from complete. These considerations, based on experimental interrelationships of the thyroid, the ovary and the adrenal cortex, are, of course, speculative and can be considered nothing more than suggestions that may stimulate further clinical studies and reports of cases.

SUMMARY

The pathologic observations in a case of osteodystrophia fibrosa combined with precocious puberty, melanotic pigmentation and severe exophthalmic goiter are presented.

30. Marine, D.; Lowe, B. H., and Cipra, A.: Influence of Glands with Internal Secretion on the Respiratory Exchange: VII. The Possible Influence of Suprarenal Involution in Newborn Infants on Heat Production, J. Metab. Research **2**: 329-339 (Sept.) 1922.

31. Jaffe, H. L., and Marine, D.: The Influence of the Suprarenal Cortex on the Gonads of Rabbits, J. Exper. Med. **38**:93-106 and 107-115 (July) 1923.

The disease of the bones is patchy and is characterized by lacunar osteoclastic resorption, fibrosis of marrow spaces, osteoblastic repair and cyst formation. The presence of islands of cartilage with bone formation at their peripheries is looked on as an extreme effort at repair. The pathologic picture resembles in some respects von Recklinghausen's disease, although the tempo of bone resorption is somewhat slower and hyperparathyroidism clearly is not present.

The important endocrine findings were a hyperplastic thyroid, thymus and lymphoid structures, mature cystic ovaries with no evidence of luteinization, a narrow, "lean" adrenal cortex, and parathyroids within normal limits. The pituitary showed basophilic hyperplasia with adenoma formation. No significant neurologic lesion was present.

The presence of exophthalmic goiter in this case and in others of this syndrome is considered suggestive. It may furnish a clue to the complex hormonal imbalance present in these cases and probably involving the gonads, adrenals, thyroid and pituitary.

News and Comment

GENERAL NEWS

Lists of Current Literature.—The Friends of the American Army Medical Library is supplying weekly lists of current medical literature, which include the publications received by that library and the articles contained in each. This service is maintained to keep up the library, and if one wishes to obtain the lists a subscription payment of $5 a year is requested. Provision is made, moreover, for microfilm copies of articles, at a cost of 25 cents for each article not exceeding twenty-five pages in length and 10 cents for each additional ten pages or fraction.

Abstracts from Current Literature

Anatomy and Physiology

THE DEVELOPMENT OF THE OLFACTORY AND THE ACCESSORY OLFACTORY FORMATIONS IN HUMAN EMBRYOS AND FETUSES. TRYPHENA HUMPHREY, J. Comp. Neurol. **73**:431 (Dec.) 1940.

Of the 13 human fetuses used in this study, 11 had been tested for their reactivity to external stimuli and photographed in moving pictures. The series ranged from 14 to 145 mm. in length. Up to the 37 mm. stage the entire fetus was sectioned. From the 49 mm. stage onward the brain was removed and sectioned separately. Some series were stained for cells and others by Bodian's silver technic. Recognition of the primordia of both olfactory and accessory olfactory formations was possible in the 26 mm. fetuses, which had a menstrual age of 8 to 8½ weeks. At this time each formation showed three layers, which apparently corresponded to the ependymal, mantle and marginal layers characteristic of the developing neural tube. From these layers there developed a laminated cortex of five layers in both formations. In the 145 mm. fetus, menstrual age 18½ weeks, the olfactory formation showed the lamination pattern as well differentiated as in the adult. In the same fetus the accessory olfactory formation was still demonstrable. Before this stage, however, beginning at the 49 mm. stage, menstrual age 11 weeks, regressive changes had appeared on one or both sides. The accessory olfactory formation is absent in the adult human brain. The development and regression of the accessory olfactory formation parallel the history of the vomeronasal organ, or organ of Jacobson, in man.

ADDISON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

Biochemistry; Bacteriology, and Pathology

RESISTANCE OF PNEUMOCOCCUS STRAINS TO SULFAPYRIDINE IN VIVO. J. MULDER, R. v. d. BERG and G. EIMERS, Nederl. tijdschr. v. geneesk. **84**:923 (March 9) 1940.

The pneumococcus strain America I can become resistant to sulfapyridine in a few days in the mouse, although the strain is originally very sensitive to the action of this drug.

The young resistant strain is at first less virulent than the sensitive strain, but after a few mouse passages it easily regains its maximal virulence.

The resistance of the strain can be made complete with the maintenance of full virulence.

The young resistant strain can cause a long-standing bacteremia in the mouse when the animal is treated with sulfapyridine. Later this phenomenon disappears.

For clinical purposes it is important to count on the possibility of the development of chemoresistance. Severe pneumococcic infections should be treated from the onset with large doses of sulfapyridine, and this treatment can perhaps be combined with advantage with administration of type-specific antiserum.

VAN CREVELD, Amsterdam, Netherlands.

Metabolism; Infant Feeding; Milk and Other Foods

OBESITY IN CHILDHOOD: V. THE FAMILY FRAME OF OBESE CHILDREN. HILDE BRUCH and GRACE TOURAINE, Psychosom. Med. **2**:141 (April) 1940.

The senior author of this paper has made several other important contributions to a better understanding of the problem of obesity in childhood. In this study

the family constellations of 40 obese children were intensively investigated. Certain characteristics, attitudes and relationships were found to be common qualities in these families.

The physical home conditions were surprisingly good, in spite of the fact that the families were on a marginal economic level. The amount of money spent for food was out of proportion to other expenses.

The fathers were weak, passive persons. They had a better relationship with their children than did the mothers, but because they lacked aggressiveness they were unable to provide positive guidance.

The mothers were emotionally immature, were resentful of society and indulged in much self pity. As children they had been subjected to material and emotional deprivation.

There was marital discord in all but a few families. The number of children per family was small. There were many induced abortions, and rejection of the children by the mother was a common attitude. Many cases of rejection were compensated for by overprotection and excessive feeding. Obesity as a symptom caused little concern to the parents except in the cases of some of the boys, and in these instances the concern was directed to the genital development.

The home life offered little security for the children, and intake of food came to be a substitute for the needed love and satisfaction. On the other hand, physical activities were eschewed because they were associated with the concept of danger, threat and insecurity. WEINFELD, Highland Park, Ill.

EXCRETION OF MELANOGEN IN BREAST MILK. H. GOTTRON and W. GERTLER, Arch. f. Dermat. u. Syph. **181**:91, 1940.

A woman aged 25 was seen in January 1938 with an enlarging reddish nodule on the right side of the back. Thormählen's test for melanogen in the urine always gave positive reactions. Melanoma was diagnosed, and roentgen therapy was used. In July 1938, during the seventh month of pregnancy, enlarged lymph nodes were present in the axilla. Thormählen's test of the urine showed a positive reaction. Severe headache and leg ache were attributed to metastases demonstrated by roentgenograms. After delivery, the breast milk gave a positive Thormählen reaction, as did the infant's urine at the age of 5 weeks. The reaction was negative while the child was fed artificially but again became positive while the child was on the breast. BECKER, Chicago. [ARCH. DERMAT. & SYPH.]

THE ELECTROCARDIOGRAM IN HYPOCALCEMIA. W. J. VAN DORP, Nederl. tijdschr. v. geneesk. **84**:811 (March 2) 1940.

In normal persons there is a constant relation between the duration of the QT interval of the electrocardiogram and the heart rate, which is best expressed by the formula of Hegglin and Holzmann (1937). A lowered calcium content of the blood is attended by a lengthening of the QT interval. This interval is also lengthened in a few other conditions, which can be differentiated by other coexisting changes in the electrocardiogram.

An observation is described of a case of parathyreoprival tetany which is of special interest because the electrocardiogram of the patient had formerly been found normal and no changes of the heart itself could be held responsible for the electrocardiographic changes. VAN CREVELD, Amsterdam, Netherlands.

Vitamins; Avitaminoses

CALCIUM AND PHOSPHORUS METABOLISM IN OSTEOMALACIA: IX. METABOLIC BEHAVIOR OF INFANTS FED ON BREAST MILK FROM MOTHERS SHOWING VARIOUS STATES OF VITAMIN D NUTRITION. S. H. LIU, H. I. CHU, C. C. SU, T. F. YU and T. Y. CHENG, J. Clin. Investigation **19**:327 (March) 1940.

Data on calcium, phosphorus and nitrogen metabolism were obtained on 4 women while they were supplying breast milk to 4 infants from whom similar

data were secured at the same time, showing an intimate relationship in the state of vitamin D nutrition between the mother and the infant during the nursing period. The 4 sets of subjects were: (1) a woman with healing osteomalacia, given an abundant supply of vitamin D, and her infant, born normal; (2) a mother with osteomalacia and tetany and her infant, with rickets and tetany; (3) a normal wetnurse and a rachitic infant born of an osteomalacic mother; (4) an osteomalacic mother, who received vitamin D during part of the gestation period, and her infant, apparently normal at birth.

The original article should be consulted for details of excellent metabolism studies showing the effects of vitamin D therapy on calcium and phosphorus storage in both the mother and the nursing infant. GUEST, Cincinnati.

CALCIUM AND PHOSPHORUS METABOLISM IN OSTEOMALACIA: X. FURTHER STUDIES ON VITAMIN D ACTION; EARLY SIGNS OF DEPLETION AND EFFECT OF MINIMAL DOSES. H. I. CHU, S. H. LIU, T. F. YU, H. C. HSU, T. Y. CHENG and H. C. CHAO, J. Clin. Investigation **19**:349 (March) 1940.

Calcium and phosphorus metabolism was studied in 3 patients with osteomalacia and in 1 normal infant born of an osteomalacic mother, during prolonged periods while the patients were on vitamin D–deficient diets. At first all showed conservative balances, but later the following changes were observed: The urinary calcium decreased and then disappeared; the fecal calcium progressively increased, and the calcium balance diminished or became negative when the calcium intake was low. Both the urinary and the fecal phosphorus increased. The serum calcium and inorganic phosphorus usually diminished only slightly during the period of observation. GUEST, Cincinnati.

OBSERVATIONS ON THE PLASMA PROTHROMBIN AND THE EFFECTS OF VITAMIN K IN PATIENTS WITH LIVER OR BILIARY TRACT DISEASE. FREDERICK J. POHLE and JOHN K. STEWART, J. Clin. Investigation **19**:365 (March) 1940.

The plasma prothrombin was reduced below normal in 47 per cent of 136 consecutive cases of disease of the liver or biliary tract. In 10 patients who exhibited abnormal bleeding the plasma prothrombin was markedly reduced. After oral administration of vitamin K and bile salts to 46 patients with a reduction of plasma thrombin, the plasma prothrombin increased in 28 patients but not in the others; the failure of the plasma prothrombin to increase after the administration of vitamin K in certain cases of jaundice was thought to be due to extensive hepatic damage. It was suggested that in the absence of obstructive jaundice, external biliary fistula or abnormal intestinal absorption, the plasma prothrombin serves as a measure of hepatic function. GUEST, Cincinnati.

VITAMIN SHOCK IN THE TREATMENT OF RICKETS. J. SCHWARZENBERG and J. COUSINO, Rev. chilena de pediat. **11**:141 (April) 1940.

On the basis of experimental work the authors assumed that the dosage for a complete cure of manifest rickets lies somewhere between 12 and 15 mg. of vitamin D_3 (calciferol), or, in other words, between 5,000 and 6,000 international (U. S. P.) vitamin D units. The authors used several different commercial preparations, one of which was given by injection. They reported on a total of 53 treated patients.

The authors found that pure crystalline vitamin D_3 (calciferol) is well tolerated by infants and does not produce toxic effects. The curative effect manifests itself rapidly and is pronounced in a short time.

There were rapid changes in the phosphorus and calcium content of the blood and in the changes in the bones. One of the infants showed tetany. In spite of the fact that the phosphorus level of the blood rose rapidly, the rise was always paralleled by a marked elevation of the calcium level. The lowering of immunity is not brought on by this type of treatment. Prolonged subsequent observation did not show a return of the disorder. SCHLUTZ, Chicago.

CLINICAL STUDIES ON VITAMIN K. HANS HULT, Nord. med. **6**:936 (May 18) 1940.

The prothrombin content of the blood in 42 cases of acute hepatitis (catarrhal jaundice) is reported. The method of Dam and Glavind (*Acta med. Scandinav.* **96**:108, 1938) was used. In 20 cases a definite decrease of the prothrombin content was noted during the most acute stage of the disease, with spontaneously increasing values when the hepatitis was improved. On administration of vitamin K, a more rapid increase of the prothrombin content occurred and at the same time an improvement of hepatic function (as determined by tests) was noted. The author is of the opinion that the hypoprothrombinemia in certain cases of acute hepatitis is due to deficient resorption of vitamin K from the intestines caused by a deficient supply of bile. WALLGREN, Göteborg, Sweden.

Hygiene; Growth and Nutrition; Public Health

ORGANIZATION AND DIRECTION OF THE DIET KITCHEN OF THE CHILDREN'S HOSPITAL AT ZURICH. G. FANCONI, Arch. de méd. d. enf. **43**:193 (July-Aug.) 1940.

In 1926, the predecessor of Fanconi, Prof. E. Feer, created a dietetic unit at this hospital, independent of the main service and the diet kitchen of the infants' pavilion, where raw fruits and vegetables especially would be properly prepared for consumption. The development of this unit since that time has been rapid, and the results have been extremely satisfactory, particularly in the management of such conditions as celiac disease and acute infections of the intestinal tract. The adaptation of its facilities has also been of great benefit in the treatment of nephritis, diabetes and obesity; the kitchen has grown to major proportions and is now centered permanently among the other dietetic divisions of this important institution. For the most part, the activities of the special cuisine are concerned with the feeding of patients beyond the age of 1 year. In addition to the diseases noted, the following disorders are discussed at length in their relation to relief through purely dietetic therapy: gastric diseases; the anemias; febrile diseases such as typhoid; epilepsy, and certain dysfunctions of the liver.

The preparation of standard dishes is fully described, and the general plan of this unique service is presented with suitable illustrations. AMESSE, Denver.

RELATION BETWEEN STATURAL GROWTH AND INTELLECTUAL DEVELOPMENT IN PARISIAN SCHOOL CHILDREN. ROUDINESCO and VIOLET, Bull. Soc. pédiat. de Paris **37**:123 (March) 1939.

The frequency of low intelligence among short children was explained on the basis of syphilis, tuberculosis and alcoholism in the parents, which usually resulted in poor hygiene in rearing children. There was no absolute relationship between intelligence and physical development. BENJAMIN, Montreal, Canada.

Prematurity and Congenital Deformities

FETAL AND NEONATAL DEATHS: A STATISTICAL ANALYSIS OF TWO THOUSAND AUTOPSIES. EDITH L. POTTER, J. A. M. A. **115**:996 (Sept. 21) 1940.

The author analyzes the results of postmortem examinations of 2,000 babies, 1,205 of these were stillborn and 795 born alive. Only those dying in the first month are included: 70 per cent of these died in the first forty-eight hours. Most of the deaths were due to harmful effects occurring during labor, conditions included in the remediable group.

The number of abnormalities noted at autopsy was increasingly high in proportion to maturity. None were present in 43.5 per cent. The particular causes found are listed.

Maternal complications are important as the cause of death, particularly when operative intervention or caudal delivery enters in.

One third of the deaths occurred before labor. Half of these were from maternal causes. For the infants dying after birth, prematurity, birth trauma and malformation were the most common causes of death and pneumonia was most important after two days.

HEERSMA, Kalamazoo, Mich.

CROUZON'S DISEASE. J. A. GALLINO and J. A. ONETO, Arch. de oftal. de Buenos Aires **14**:1010 (Dec.) 1939.

A case is reported of Crouzon's disease with cranial deformity, exophthalmos, atrophy of the optic nerve, divergent strabismus and maxillofacial deformity. The text is illustrated with photographs and roentgenograms. The literature is reviewed, and statistics are given as to the frequency of different elements in the deformity.

The authors distinguish three stages: (1) dysostosis commencing shortly after birth, with infiltration of the cranial sutures and development of synostosis; (2) appearance of compensatory ectasia of the cranial contents; (3) cranial compression and the dysostosis syndrome.

The atrophy of the optic nerve has been explained by papillary stasis and by compression in the optic canal.

The exophthalmos is due to reduction in the depth of the orbit.

C. E. FINLAY. [ARCH. OPHTH.]

EXPERIENCES WITH OPERATIONS FOR CLEFT PALATE. K. E. HERLYN, Beitr. z. klin. Chir. **169**:397, 1939.

Herlyn describes the standard technic of operation for cleft palate and the postoperative management. He emphasizes the fact that plastic operations on harelips should be performed early, so that repair of cleft palates may be done toward the end of the second year of life.

RUBIN, Boston.

ASSOCIATION BETWEEN CLEFT PALATE AND OTHER CONGENITAL ANOMALIES, ESPECIALLY THOSE OF THE VETEBRAL COLUMN. C. H. SCHRÖDER, Beitr. z. klin. Chir. **169**:402, 1939.

Schröder discusses the family trees of several families and shows that there is an association between cleft palate and other anomalies. He describes various types of anomalies in the vertebral column (spina bifida, etc.).

RUBIN, Boston.

BRACHYDACHTYLY AND CONGENITAL SPHEROPHAKIA A SYSTEMIC DISEASE: REPORT OF CASES. O. MARCHESANI, Klin. Monatsbl. f. Augenh. **103**:392 (Oct.-Nov.) 1939.

Arachnodachtyly with ectopia of the lens constitutes Marfan's syndrome. Marchesani reports on a reverse syndrome, brachydachtyly coupled with spherophakia (microphakia; congenital globular lens). The genealogy of two families is given. In the first family a boy, aged 8, had typical microphakia complicated with glaucoma, which could not be conquered by posterior sclerotomy, two cyclodialyses, extracapsular extraction of the lens and discission. The boy was short, with shortened extremities and broad hands, feet, fingers and toes. He was brachycephalic, intelligent and lively. The patient in the second family was a man aged 36, short, stocky and brachycephalic. He had short hands, feet, fingers and toes. The vision of both eyes was reduced to one tenth of the normal. The right lens had been removed. Myopia (18 D.) existed in the left eye; glaucoma with deep excavations of the disks was present in both eyes. One brother and 1 sister showed globular lenses and brachydachtyly. Two sisters and 1 brother were free from the syndrome, but the brother's children showed nystagmus, amblyopia and other ocular symptoms.

K. L. STOLL. [ARCH. OPHTH.]

CONGENITAL HYPERTROPHY. G. W. KASTEIN, München. med. Wchnschr. **88**:273 (March 7) 1941.

From a detailed study of 5 cases of hemihypertrophy, Kastein concludes that the condition is due to a disturbance of the peripheral vegetative nervous system. He states, however, that he has no postmortem material to substantiate his theory. It is based on the presence of certain pigment disturbances (such as vitiligo), hemimydriasis, hypoplasia of the shoulder muscles, bladder disturbances and the distribution of telangiectases which occurred in his cases.

BRAHDY, Mount Vernon, N. Y.

ADHERENCE OF PLACENTA TO HEAD OF CHILD; ADHERENCE OF AMNIOTIC TISSUE TO CENTRAL NERVOUS SYSTEM. G. ILBERG, Ztschr. f. Geburtsh. u. Gynäk. **121**:126, 1940.

The gross and histologic appearances of several monsters presenting these anomalies are described.

ADAIR, Chicago.

BIRTH OF A THORACOPAGUS. A. BUTTERMANN, Ztschr. f. Geburtsh. u. Gynäk. **121**:150, 1940.

The technic for delivery of this form of monster is described.

ADAIR, Chicago.

MALFORMATIONS OF ABORTED FETUSES: THEIR CAUSES AND CLINICAL SIGNIFICANCE. K. W. SCHULTZE, Ztschr. f. Geburtsh. u. Gynäk. **121**:242, 1940.

The political implications of abortions are stressed, since statistics show that with 1,300,000 births in "old Germany" about 220,000 abortions occur yearly, of which approximately 100,000 are preventable. Many of these are related to an inadequate corpus luteum factor and can be prevented by addition of this substance. In 23 per cent of the cases studied a lack of corpus luteum hormone or of vitamin E was considered as the causative factor, and in 37 per cent developmental abnormalities in the ovum were felt to be responsible.

In the study of fetal abnormalities, the placenta must also be studied. Many pathologic reports and an extensive and excellent bibliography are part of this careful study.

ADAIR, Chicago.

Newborn

EPIDEMICS OF DIARRHEA IN THE NEWBORN. WALTER D. LUDLUM, New York State J. Med. **40**:1238 (Aug. 15) 1940.

Ludlum believes that epidemics of diarrhea in the newborn are caused by poor technic in the management of the nursery; also that transference is by droplet infection and infected bottle nipples. Infection can be prevented by proper masking of attendants and proper sterilization of bottle nipples.

AIKMAN, Rochester, N. Y.

DIPHTHERIA IN THE NEWBORN AND IN THE NURSLING. J. P. GARRAHAN, R. RODRIQUEZ and H. LOIZAGA, Arch. argent. de pediat. **11**:119 (Feb.) 1940.

This article is based on a recent epidemic in the newborn. Diphtheria is comparatively rare in infants under 1 year old. Most of them have a considerable immunity against the disease. In hospital services, however, and in maternity homes, epidemics may occur. It has been established that a small percentage of the newborn (approximately 10 to 15) are receptive to the infection.

Widespread immunization against diphtheria has reduced the number of receptive infants considerably. Infection with diphtheria in the domestic environment of the home is very infrequent. The situation, especially for the newborn, is some-

what different in hospitals, where infection is easily spread and there is greater danger from carriers. It is important that possible carriers be eliminated from the hospital personnel.

SCHLUTZ, Chicago.

ICTERUS GRAVIS IN THE NEWBORN. C. RUIZ, Arch. argent. de pediat. **11**:152 (Feb.) 1940.

The author reports 7 cases of icterus gravis in newborn infants. In 5 of the cases there were hematologic changes. In 2 of them there were no clinical pathologic changes. At autopsy in the latter 2 cases no pathologic changes were noted in the hemopoietic organs, such as the liver and spleen.

In these 2 cases blood transfusions were not given. In 3 of the 5 cases in which there was severe erythroblastosis, multiple transfusions were given. The patients so treated showed a transitory improvement following the transfusion, but all of them died. In the 2 remaining cases, in which transfusions were not given, 1 patient died and 1 recovered. The author is of the opinion that erythroblastosis is not an absolutely pathognomonic finding in these cases. In some of them it is the preponderant symptom; in others it may not be present. The cause of the condition is still very obscure.

SCHLUTZ, Chicago.

DIAGNOSIS AND PROGNOSIS OF INTRACRANIAL HEMORRHAGES OCCURRING AT BIRTH. SIEGFRIED LIEBE, Monatschr. f. Kinderh. **83**:1, 1940.

The diagnosis of intracranial birth hemorrhages in newborn infants by means of testing for bilirubin in the blood and spinal fluid according to Catel is developed methodically with the help of a more exact method. The reliability of the method was examined in 68 cases controlled by autopsy. The limits of the diagnostic method are critically discussed. No conclusions with regard to intracranial hemorrhage in an individual case can be made from the type of birth; a pathologic birth must not be overestimated. Premature children are not particularly the victims of intracranial hemorrhage. All clinical symptoms that accompany intracranial hemorrhage may also occur in children without any such hemorrhage. Xanthochromia of the spinal fluid is never decisive; absence of demonstrable albumin (negative Pandy reaction) does not absolutely exclude hemorrhages. Changes of the blood picture of newborn infants are not characteristic. There is no certain connection between Little's disease and birth injury and no certain proof of the causal connection between intracranial hemorrhage and imbecility—just as there is slight connection between intracranial hemorrhage and hydrocephalus, as has been proved by section. Some neurologic diseases (athetosis-like movements and twitching of the face, hemiplegia spastica infantilis and disturbances of the muscle tonus) most likely occur in connection with intracranial hemorrhages due to trauma at birth.

NEURATH, New York.

PATHOLOGIC AND ANATOMIC CONTRIBUTIONS FROM THE MONOGRAPH OF E. KEHRER: THE INTRACRANIAL HEMORRHAGE OF THE NEWBORN. R. BENEKE, Ztschr. f. Geburtsh. u. Gynäk. **120**:105, 1940.

The chief contributions from the monograph of Kehrer are presented. Antepartum and intrapartum hemorrhage are dealt with, as well as the anatomic basis for extradural, dural, leptomeningeal, intracerebral, intracerebellar, ventricular and basal intracranial hemorrhage. A careful exposition of the technic for section and examination of the material is reviewed. Another section discusses the predisposition of the fetus in utero to hemorrhage due to specific tissue injury, such as occurs in dietary deficiencies, intrauterine asphyxia and hypertensive diseases. Still another factor discussed with regard to the causes of intracranial hemorrhage is the prevalence of operative obstetrics. A prophylactic system for the control of intracranial hemorrhage in the newborn is developed from this material, with political implications stated for totalitarian governments.

POTTER and KASDON, Chicago.

PERSISTING OPISTHOTONOS IN THE NEWBORN AFTER BIRTH WITH FACE PRESENTATION. B. OTTOW, Ztschr. f. Geburtsh. u. Gynäk. **121**:39, 1940.

Kehrer has described the changes accompanying long-standing face presentation: dolichocephaly, asymmetry of the ears, torticollis, increased bowing of the clavicles and persisting deflection position of the head. Primary face presentations, i. e., those present from early development, are differentiated from the secondary, i. e., those resulting from deflection presentations at parturition. The diagnosis of the former can be made roentgenologically. The persistent forms of opisthotonos are usually of the primary type and are related to atrophic changes in the musculature of the neck, due to disuse, to atrophy or to primary developmental failure.

ADAIR, Chicago.

SYMMETRIC LINE DEFECTS IN THE SKIN AT BIRTH. W. REISS, Ztschr. f. Geburtsh. u. Gynäk. **121**:67, 1940.

Eleven cases of congenital symmetric line defects in the skin of the hands are described. The characteristics of such defects are: (1) definite symmetry, (2) localization to a single line extending upward from the base of the forefinger on the ulnar side of the lower part of the arm or in a similar location on the leg, (3) appearance similar to a skin abrasion. The changes in the histologic structure are not unlike those produced by injury. The author feels that the cause is an endogenous developmental defect plus an exogenous factor, such as injury during the last part of pregnancy.

ADAIR, Chicago.

TEMPORARY OBSTRUCTIVE ICTERUS AND OCCURRENCE OF GALLSTONES IN THE NEWBORN. E. HITTENHEIN, Ztschr. f. Kinderh. **61**:696 (April 26) 1940.

The author reports the case of a newborn infant in whom profound icterus developed. On the nineteenth day of life, after several hours of extreme restlessness and evidence of abdominal pain, a bile-stained stool was passed. Although no gallstone was found, the author assumes that one may have been present. A review of the literature revealed that cholelithiasis in infants is more common than is ordinarily supposed. In the case reported a rather severe anemia and opisthotonos were present, and the author concludes that the child probably had icterus gravis without erythroblastosis or a transitional form to newborn anemia with damage to the cerebral nuclei (kernicterus).

SIEMSEN, Chicago.

CAUSES OF FEVER OF NEWLY BORN INFANTS. Ö. KERPEL-FRONIUS and D. KAMOCSAY, Orvosi hetil. **84**:245 (May 11) 1940.

In 238 of 3,037 newly born infants (i. e., in 7.84 per cent) the authors found a temperature which was higher than 37.5 C. (99.5 F.). On the basis of causation this fever can be separated into two types: (1) fever due to infection (24.7 per cent), mostly catarrhal infection brought in by visitors; (2) "aseptic fever." The aseptic fever has many causes. True dehydration fever occurred only in 38.7 per cent of cases. The term "dehydration fever" can be used only in cases in which loss in weight is accompanied with fever which subsides promptly when fluid is supplied in proper amounts. In the majority of cases aseptic fever has some cause other than dehydration. There are many possible causes: the *Schreihyperthermie* described by Rietschel; swallowing of amniotic fluid; perhaps the change of bacterial flora of the meconium. It is interesting that newly born infants with "complicated birth" had a higher incidence of fever (18.1 per cent) than infants with normal birth. Dehydration fever reaches its highest point mostly on the third day after birth, whereas aseptic fever and fever caused by infection are rather prolonged.

GÖTTCHE, Budapest, Hungary.

HYPOPROTHROMBINEMIA NEONATORUM. LEIF SALOMONSEN, Nord. med. **7**:1309 (Aug. 3) 1940.

The delayed clotting time in newborn infants, especially in those suffering from hemorrhagic disease of the newborn, is due to a hypoprothrombinemia which depends on a deficiency of vitamin K. This deficiency is probably caused by unsatisfactory production of the vitamin in the intestines of the infant. The hypoprothrombinemia can be prevented by ingestion of small amounts of cow's milk mixtures given from the first day of life, beginning two hours after birth.

WALLGREN, Göteborg, Sweden.

PREVENTION OF HEMORRHAGIC DISEASE OF THE NEWBORN. K. K. NYGAARD, Nord. med. **7**:1535 (Sept. 14) 1940.

By administration of vitamin K to a pregnant or a lactating woman the vitamin is transmitted to the fetus or to the infant respectively. The level of prothrombin in the newborn infant attained by this method is lower than if the same amount of the vitamin is given directly to the infant. The author recommends, however, that 10 mg. of vitamin K be given daily to pregnant women during the last one to two weeks before parturition.

WALLGREN, Göteborg, Sweden.

Acute Contagious Diseases

RETINAL CHANGES WITH MARKED IMPAIRMENT OF VISION IN MEASLES. F. R. SCHLOSSBERG and M. PRIZER, Am. J. Ophth. **23**:998 (Sept.) 1940.

Schlossberg and Prizer report on a 6 year old girl in whom the vision in each eye was entirely lost five days after the onset of measles. Ophthalmoscopic examination revealed blurred disk margins with some swelling, moderately engorged veins and small and threadlike arteries. Throughout the fundi were numerous small round hemorrhages. Several months later there was postneuritic atrophy, a macular lesion was present, there were attenuated vessels in both fundi and the vision was 4/200 in the right eye and 3/200 in the left. No definite diagnosis was made, several ophthalmologists differing.

W. S. REESE. [ARCH. OPHTH.]

SPREADING OF VACCINE IN NASAL VACCINATION. EMIL WEISS, Arch. Otolaryng. **33**:623 (April) 1941.

The author discusses at length the application of antigenic material to the upper respiratory tract, which presents an easily accessible absorptive surface for inoculation. The risk of the development of pneumonia following inoculation is discussed and stated to be negligible if the amount of material used is limited to one spray or one drop. Advantages of such inoculation are presented. Laboratory experiments are outlined.

GREENWOOD, Chicago.

EPIDEMIC CEREBRAL MENINGITIS (MENINGOCOCCIC). KALEI K. GREGORY, EDWARD J. WEST and RAYMOND E. STEVENS, J. A. M. A. **115**:1091 (Sept. 28) 1940.

One hundred and thirteen patients with meningococcic meningitis were treated over a period of three years by different methods. Comparing the results obtained by intrathecal and intravenous injection of meningococcus antiserum with those obtained by intravenous injection of antitoxin, the authors were unable to confirm Hoyne's results. They had similar mortality rates (about 40 per cent) with all the methods.

Later, when they used sulfanilamide alone, the rate was reduced to 17 per cent. They feel that intrathecal methods can largely be discarded, because of the diffusibility of sulfanilamide.

Two complications developed in the series, paralysis of the ocular muscles and deafness. No complications developed in the 29 cases in which sulfanilamide was given.

HEERSMA, Kalamazoo, Mich.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **56**:985 (May 9) 1941.

The incidence of influenza for the period of March 23 to April 19 decreased 50 per cent from the incidence for the preceding four weeks but was still 30 per cent over the median incidence. This was mainly in the South Atlantic and the western part of the South Central region. The incidence of measles rose to 219,000 cases, the highest for this period on record. The increase affected all regions except the Pacific area and New England. The incidence of poliomyelitis was raised slightly over the seasonal expectancy by 14 cases reported from Florida. Whooping cough also had a high incidence in all regions except the Middle Atlantic area. All other diseases were below the median. The average mortality from all causes was 12 per thousand, which is slightly below the 1938 to 1940 average (12.4).

SANFORD, Chicago.

"SPORADIC" POLIOMYELITIS. L. L. LUMSDEN, Pub. Health Rep. **56**:992 (May 9) 1941.

The author analyzes 34 cases of sporadic poliomyelitis reported in Tennessee in 1939, and 8 cases reported in the first six months of 1940. He questions whether there has been in Tennessee since 1936 a single case of poliomyelitis etiologically identical with that which occurs at times in the United States in outbreak or epidemic form. He concludes that intensive studies of "sporadic" poliomyelitis situations, as well as epidemics, by competent observers and centralized public health agencies would reveal a considerable proportion of erroneous diagnoses, especially in nonepidemic seasons.

SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **58**:1191 (June 6) 1941.

For the period of April 20 to May 17 the incidence of influenza dropped to less than half of the figure for the preceding four week period but was still 40 per cent above the median figure. Measles also decreased, but the incidence was still the highest on record, with 172,184. Poliomyelitis and whooping cough were about 50 per cent above median incidence. All other diseases were below. The average mortality from all causes was 11.3 per thousand, which is slightly below the average.

SANFORD, Chicago.

SCARLET FEVER IN A PUBLIC SCHOOL. J. K. BOSTOCK, Brit. M. J. **2**:144 (July 27) 1940.

The author reports an epidemic of infection with hemolytic streptococci which occurred in a public school. In almost every case swabs were made and typed according to the Griffith method, and it was revealed that in 64 of 87 cases of this infection the causative organism was due to type 18. In the remaining 23 cases the streptococci were nine other different types. Scarlatiniform rashes occurred in a proportion of about 1 to 13 cases in the cases of infection with type 18 streptococci and in about 1 in 4 cases of infection with the other various types. It was noted that the infection with the type 18 organisms were the only ones which showed epidemic quality. Two cases were reported which demonstrated that immunity to one type of streptococcus did not give immunity to a different type. The author's conclusions are as follows:

"It seems reasonable to conclude that the production of the rash in this epidemic depended on two factors at least: first, on the individual reaction of the patient to each type and not to any variation in the character of the specific type; and, secondly, on the rash-producing properties of each individual type, which appeared to be greater in the non-epidemic strains.

"Many, if not all, types of haemolytic streptococcus seem to be capable, in certain circumstances, of producing the rash of scarlet fever.

"The production of the rash had no effect on the course of the disease and these cases were almost without complication. It was therefore regarded as of no special significance. Epidemic quality was shown to a high degree in one type only, and the virulence of this infection remained low. Other types presented the usual low degree of infectivity.

"A highly specific immunity was apparently set up on two occasions for individual types, as shown by second attacks by dissimilar types at short intervals.

"Scarlet fever is a misleading term which suggests a distinction that does not exist between different haemolytic streptococcal infections."

ROYSTER, University, Va.

MEDIASTINAL EMPHYSEMA IN THE COURSE OF MALIGNANT DIPHTHERIA: CASE REPORT. G. PAISSEAU and TEYSSIER-COMMERSON, Arch. de méd. d. enf. **43**:218 (July-Aug.) 1940.

Mediastinal emphysema developed in a boy of 6 years after a severe attack of diphtheria in which instrumental damage to the larynx could be excluded.

The patient was admitted to the hospital on the tenth day of the disease, without having had any treatment. There were an abundant false membrane covering the pharynx and uvula, bilateral cervical adenitis, hoarseness and cough. Examination revealed also great prostration with low blood pressure and albuminuria. The temperature was not elevated; epistaxis was reported before admission. The boy was given 40,000 units of antidiphtheritic serum on the first day and 30,000 units on the day following, with cardiac tonics and strychnine in large doses. The symptoms of suffocation were promptly relieved, but prostration, azotemia and nasal hemorrhage continued.

On the sixth day, with the general condition improving, another complication presented. Auscultation revealed over the entire precordial area large dry superficial rales giving the impression of snowy crepitation and resembling somewhat the phenomena of subcutaneous emphysema. Palpation of the entire region, however, gave distinctly negative results; the rales became synchronous with the heart beat and with the movements of respiration. Fever, cyanosis and dyspnea were absent. Collapse and death occurred on the twelfth day.

Autopsy revealed an extensive emphysema involving the mediastinum which followed two semicircular ulcerations on the lateral aspect of the inferior lobe of the left lung. Manifestly an alveolar rupture occurred near the surface of the lung and established infiltration of air in the subpleural cellular tissue.

AMESSE, Denver.

OBSERVATIONS ON THE TEMPERATURE CURVE IN MEASLES. I. H. ALANTAR, Arch. de méd. d. enf. **43**:225 (July-Aug.) 1940.

As fever constitutes one of the chief symptoms of all infections, one may derive valuable conclusions from its study, for determining not only the diagnosis but the prognosis and the probable duration of the disease.

With only secondary value in cases of such diseases as chickenpox and whooping cough, the symptom of fever is of primary importance with measles. The author has made an intensive investigation of the temperature range in this infection and believes that even the slight rise that may be noted during its earliest stages has a distinct bearing on prophylaxis, particularly in orphanages and similar institutions.

The diversity of the thermic curve in different cases and with different epidemics is noted in detail.

AMESSE, Denver.

EXPEDIENCY OF PREVENTIVE INJECTION OF DIPHTHERIA ANATOXIN INTO CONTACTS, WITH CONSIDERATION OF THREE CASES OF MALIGNANT DIPHTHERIA. PAUL GIRARD, LOMBROSO and PROVANSAL, Bull. Soc. pédiat. de Paris **37**:131 (March) 1939.

The cases of 3 children who were exposed to malignant diphtheria and who had not received any antidiphtheritic inoculations are reported. They were each given 1.0 cc. of anatoxin, but severe diphtheria developed soon afterward. Two, who were given antitoxin on the fourth and sixth days respectively of the disease, died, while the third, who received it on the second day, recovered. Obviously, a dose of anatoxin administered to a child who has been in contact with diphtheria and who has not been immunized previously does not prevent the disease from developing nor does it stimulate the formation of adequate antitoxin to be effective in its treatment. If anatoxin is given during an epidemic, the children should be observed carefully and at the first signs of the development of diphtheria antitoxin should be injected.

BENJAMIN, Montreal, Canada.

VACCINATION AND ACUTE ANTERIOR POLIOMYELITIS. PASQUEL R. CERVINI and JUAN V. TISCORINA, An. Soc. puericult. de Buenos Aires **7**:120 (April-June) 1940.

Joaquin, J. V., aged 18 months, was vaccinated on May 8, 1940, on the left arm. On May 18 to 20 he had high fever, followed by paralysis of the legs. The picture was clear, and symptomatically the condition should have been considered as a flaccid paraplegia of the legs occurring at the height of the vaccination reaction. The interpretation is complex. At the time the authors were making the observations they encountered 3 cases of poliomyelitis, which might make acceptable the theory of simple coincidence of the two processes. But their observation fits so exactly the succession of facts reported in other publications that they accepted another explanation. The question was: Are the virus and the vaccine localized in the anterior horn cells of the lumbar enlargement? The opinion of the majority is that vaccine alone favors infection with neurotropic virus, which is occasionally in the air or already latent in the body of the vaccinated person.

At any rate, the case shows that vaccination is not always innocuous. The authors advise no vaccination during an epidemic of poliomyelitis. The recuperation in the case has been so rapid and uniform that they hope for total cure.

GIFFEN, Toledo, Ohio.

TRYPANOCIDAL SUBSTANCE IN SERUM IN SCARLET FEVER: INVESTIGATION CONCERNING A PARTIAL FUNCTION OF THE LIVER IN CHILDREN WITH SCARLET FEVER. JOSEF STRÖDER, Arch. f. Kinderh. **118**:1 (Sept. 26) 1939.

The trypanocidal substance which is present in normal human serum is diminished in the serums of patients with damage to the liver. The capability of the liver to produce antibodies is diminished. The serums of 8 children with scarlet fever with suspected involvement of the liver were examined, and the concentration of the trypanocidal substance was found to be as high as in normal serum.

ARON, Chicago.

CRITICAL CONSIDERATIONS AND INVESTIGATIONS OF VALUE OF PROPHYLACTIC STROPHANTHIN TREATMENT FOR TOXIC DIPHTHERIA. J. STRÖDER and S. ROUFOGALIS, Ztschr. f. Kinderh. **61**:681 (April 26) 1940.

There is considerable difference of opinion regarding the prophylactic value of digitalis glucosides in general and for infectious diseases. The mechanism of damage by diphtheria toxin is also uncertain.

The authors were unable to verify Dixon and Meyer's favorable results with guinea pigs. Strophanthin hastened death. Treatment of animals with strophanthin before administration of diphtheria toxin was ineffective.

Experiments on frogs gainsay a direct effect of diphtheria toxin on the cold-blooded heart.

SIEMSEN, Chicago.

POSTPERTUSSIS MENINGOENCEPHALITIS. P. A. VILANSKY, Vrach. delo (no. 7-8) **22**:551, 1940.

The author discusses the pathogenesis of postpertussis encephalitis and presents 2 case reports. He points out the rarity with which neurologic complications occur in pertussis and cites the following autopsy statistics from a Moscow clinic for the years 1925 to 1936. Among 169 cases of death following pertussis, pneumonia was found in 90 per cent, capillary bronchitis in 1.2 per cent, tuberculosis in 8.2 per cent and all other complications, including those belonging to the central nervous system, in 0.6 per cent. The pathogenesis of neurologic complications of pertussis is still a matter of controversy. It is not yet known whether there are specific toxic or inflammatory lesions caused by the pertussis virus or whether the cerebral lesions are brought about by disturbances of circulation of blood or cerebrospinal fluid without inflammatory changes.

The first case reported by the author is that of a 6 year old child in whom the meningoencephalitic symptom complex developed at the height of the paroxysmal stage of his pertussis. It was manifested by severe headache, vomiting, ataxia, weakness of the extremities, rigidity of the neck, a positive Kernig sign, horizontal nystagmus and paresis of the abducens and facial nerves, the paresis of the latter being of the peripheral type. Lumbar puncture revealed a colorless spinal fluid under increased pressure, with lymphocytosis, strongly positive Pandy and Nonne-Apelt reactions and a sugar content of 0.05 per cent. A complete clinical recovery took place within a few weeks, and there were no positive neurologic findings even after a one year period of observation.

The second case was that of a woman aged 23 who had pertussis at the age of 8 years. There developed during the height of the paroxysmal stage, i. e., about the fourth week of the disease, fever, severe headache, vomiting and stupor diagnosed as meningitis at the time. Five days later the patient had a typical epileptiform attack manifested by a general convulsive seizure, sharp turning of the head to the left and biting of the tongue. Since that time the patient had been having periodic and typical grand mal attacks with an aura manifested by a weakness of the right foot and hand. No outstanding positive neurologic findings were observed except paresis of the right facial nerve of the central type and slight changes in some of the tendon reflexes.

The author feels that the clinical and spinal fluid findings in both patients speak for a postpertussis meningoencephalitic symptom complex, followed in the first case by recovery and in the second by development of epileptic seizures resulting from postencephalitic changes in the left cerebral hemisphere.

BODER, Los Angeles.

EXPERIMENTAL AND CLINICAL STUDIES ON IMMUNIZATION WITH DIPHTHERIA ANATOXIN. T. KOGO, Acta pædiat. japon. **47**:17 (Jan. 20) 1941.

Kogo attempted to compare the relative effects of diphtheria anatoxin administered by various routes on antibody formation in experimental animals and in children. In the guinea pig the author was able to establish the development of the diphtheria antibody in relatively high titer, as determined by the Schick test, following administration of anatoxin by percutaneous, nasal, ophthalmic and oral routes. In healthy, normal children with positive reactions to the Schick test, the most effective route for diphtheria immunization was found to be the intranasal, and the least effective the percutaneous, application of anatoxin ointment, while the oral administration gave the intermediate result. Although

the effect was not demonstrated in all instances, the author concluded that instillation of anatoxin by the nasal route is the most convenient and reliable method.

KATO, Chicago.

EPIDEMIOLOGY OF MENINGOCOCCOSIS AND POLIOMYELITIS ANTERIOR ACUTA. M. E. KULSDOM, Nederl. tijdschr. v. geneesk. **84**:398 (Feb. 3) 1940.

From a study of the occurrence of meningococcic infection it becomes acceptable that clinical cases of this infection are always independent casualties, in which the meningococcus has succeeded in overpowering an organism lacking the normal forces of defense. This fact and knowledge of the distribution of meningococci among human beings give rise to the assumption that biologically the symbiosis of man and the meningococcus can be characterized as commensalism. A study of statistics and literature on acute anterior poliomyelitis produces data in support of the view that for the virus of this disease considerations similar to those for the meningococcus are valid.

VAN CREVELD, Amsterdam, Netherlands.

INFLUENCE OF VIRULENCE AND ORIGIN OF THE VACCINE VIRUS ON THE OCCURRENCE OF EXPERIMENTAL ENCEPHALITIS. J. D. VERLINDE, Nederl. tijdschr. v. geneesk. **84**:702 (Feb. 24) 1940.

Encephalitis can be produced in dogs by vaccination of the animals during a latent guanidine intoxication. The virulence of three different strains of dermovaccine appeared not to exert any influence on the occurrence of encephalitis. Neurovaccine was more encephalitogenic than the dermovaccine. In herbivores encephalitis could not be provoked by the same method, not even in calves after vaccination with original vaccine lymph. With regard to the favorable results sometimes observed with liver treatment in spontaneous encephalitis of the dog, the blood picture of the dogs with experimental encephalitis was specially studied; no specific deviations were found, however.

VAN CREVELD, Amsterdam, Netherlands.

EVACUATION AND MEASLES. H. I. DE RUITER, Nederl. tijdschr. v. geneesk. **84**:1297 (April 6) 1940.

Outbreaks of measles under the conditions of evacuation, which are much to be dreaded in view of the overcrowding, should be kept under check with convalescent serum. Less efficient would be protection with large doses of parents' blood; this method is advisable in case of lack of sufficient serum. It must be kept in mind that under these special conditions enough serum should be injected to procure complete protection. For this a considerable stock of serum is required. In order to provide such a stock an appeal is made to the civil doctors for the accomplishment of this plan, in cooperation with the state institute of public health.

VAN CREVELD, Amsterdam, Netherlands.

SULFANILAMIDE IN TREATMENT OF SCARLET FEVER. C. M. KRÖGER-WIBAUT and D. HERDERSHCÊE, Nederl. tijdschr. v. geneesk. **84**:2341 (June 22) 1940.

Sulfanilamide given in the small and harmless doses so effective in combating erysipelas was found to be quite useless against scarlet fever. No action was seen either on the duration of the initial stage or on the frequency of complications. In the treatment of otitis media and rhinitis also the authors' results were not favorable, though their experiences with the drug in treatment of these complications were rather limited. Perhaps larger doses might be given, but not until the rhinologist's advice has been gained on the desirability of removal of possibly present adenoids.

VAN CREVELD, Amsterdam, Netherlands.

Acute Infectious Diseases

TWO CASES OF CEREBRAL RHEUMATISM IN CHILDREN ENDING FATALLY. J. CHAPTAL and J. BARNAY, Bull. Soc. pédiat. de Paris **37**:140 (March) 1939.

Two cases of rheumatic disease with cerebral symptoms believed to be due to encephalitis are reported. No necropsies were performed. The treatment advised was intravenous injection of salicylates and cold baths.

BENJAMIN, Montreal, Canada.

SALMONELLA INFECTIONS IN INFANCY. E. HORMAECHE, C. E. PELUFFO and P. L. ALEPPO, Arch. de pediat. d. Uruguay **11**:8 (Jan.) 1940.

Salmonella infections are very infrequent in infants, especially during the first year of life.

Of 177 infants from whom the organism was isolated, 152 carriers showed no intestinal disorder. All of the others showed varying degrees of subacute or acute enteritis, in some instances of the malignant type. Of 339 infants with enteritis who were examined, salmonella infection was present in about 18 per cent.

Many of the infants produced specific agglutinins during the first year of life. The agglutinins appear much later in the infection, however, than they do in adults.

Children seem to be more susceptible to salmonella infection than adults.

SCHLUTZ, Chicago.

ACUTE ENCEPHALITIS IN COURSE OF SALMONELLA INFECTION. J. R. MARCOS and S. MENDIVIL, Arch. de pediat. d. Uruguay **11**:36 (Jan.) 1940.

The authors report a case of acute encephalitis in a child 5 months old who had a salmonella infection. The disorder started with diarrhea, fever and convulsions.

The encephalitis was manifested by generalized hypertonia, mydriasis and convulsive seizures accompanied by trismus and cyanosis.

Salmonella was isolated from the stool, and agglutinin reactions for it were positive. In addition to this disorder, the infant had a chronic otitis, rhinopharyngitis and a pyoderma. The patient made a complete recovery.

SCHLUTZ, Chicago.

PURULENT MENINGITIS IN AN INFANT WITH POSITIVE CULTURE OF SALMONELLA "TYPHI MURIUM" IN THE SPINAL FLUID. E. PELUFFO, A. R. GUERRA and P. ALEPPO, Arch. de pediat. d. Uruguay **11**:48 (Jan.) 1940.

The authors report this rare condition in an infant 6 months old. The disorder began with fever, severe vomiting and diarrhea. Marked hyperthermia developed. Profuse diarrhea continued, and edema and acute purulent meningitis developed. The infant died forty-eight hours after admission to the hospital. Culture of the blood and of the cerebrospinal fluid showed Salmonella "typhi murium," and the same organism was grown from the intestinal mucosa and the mesenteric glands.

At autopsy, tuberculous lesions were found in the mesenteric and in the tracheobronchial lymph nodes.

SCHLUTZ, Chicago.

BRUCELLOSIS IN THE CHILD. J. D. LUQUE, Rev. chilena de pediat. **11**:56 (Jan.) 1940.

Brucellosis, which at one time was confined almost exclusively to the Mediterranean area, has in recent years had a considerable geographic extension. It has become a world sanitary problem.

The duration of the illness is from one-half to two years. In Chile almost 40 to 50 per cent of the cattle are infected with Brucella. In that country the author

has the impression that both in animals and in human beings the disease is more prevalent in early than in adult life. The infection can occur in various ways: In southern Chile among the peasantry it is often the custom to allow the infant to nurse directly from the udder of an animal. Or the infant is allowed to play on the floor of the barn and in that way may through direct contact introduce the organism through the mouth, particularly if the barn floor contains manure of the diseased animal.

A large source of infection is through the milk of diseased cattle or through the breast milk of a diseased mother. The incubation period is between five and twenty days. The fever is obscure and of the undulant type. There is profuse perspiration. Severe constipation develops. Rheumatic pains are often complained of. The child will show splenomegaly, tracheobronchitis and pronounced anemia. Blood culture and agglutination and intradermal tests establish the diagnosis. A mortality of 3 per cent is usual among the infected children. Neoarsphenamine is used as therapy, and also sulfanilamide.

SCHLUTZ, Chicago.

Chronic Infectious Diseases

NATURALLY OCCURRING TUBERCULOSIS IN DOGS AND SOME OTHER SPECIES OF ANIMALS. R. LOVELL and E. G. WHITE, Brit. J. Tuberc. **34**:117 (July-Oct.) 1940.

Autopsies on 453 dogs from the poorer sections of London revealed the presence of tuberculosis in 325 of the animals, an incidence of 46 per cent. Twenty-two of these were examined bacteriologically, and tubercle bacilli were isolated from 13 by direct means and from the remainder by guinea-pig innoculations. The human type of organism was found in 18 cases and the bovine type in 4. The mesenteric lymph nodes were involved in all of the infections due to the bovine type. In 7 infections of the human type the primary lesion was situated in the alimentary tract. The primary lesion was probably alimentary in 5 of the remaining cases, while in the others it might have been either respiratory or alimentary or both. Healed tuberculosis and calcification are rarely found in the dog. The number of tubercle bacilli found in sections and smears is usually small, except in tuberculous pyelonephritis, in which they are extremely numerous.

In the case of but 3 of the animals was a definite history of tuberculosis in the owner or his family found. It has been noted that the incidence of tuberculosis in dogs belonging to the proprietors of restaurants and public houses is very high.

The chief sources of danger in the transmission of infection to man lie in the sputum and urine. In dogs suffering from tuberculous pyelonephritis the urine is likely to be heavily infected.

EUGENE H. SMITH, Ogden, Utah.

TUBERCULIDS IN CHILDREN. P. W. SCHMIDT, Arch. f. Dermat. u. Syph. **181**:357, 1940.

In a cooperative study by dermatologists and pediatricians, clinical, immunologic and microscopic observations are presented of several types of tuberculids seen in 12 patients. The diagnoses were: (1) and (2) lichen scrofulosorum, (3) circinate tuberculosis lichenoides, (4) eczematoid tuberculid following varicella, (5) lichenoid tuberculid, (6) papulonecrotic tuberculid, (7) papulopustular tuberculid, (8) miliary tuberculosis, (9) sarcoid (Boeck) and (10), (11) and (12) submiliary tuberculosis in children with tuberculous meningitis.

The authors believe that microscopic study aids in differentiation and in determining the prognosis.

BECKER, Chicago. [ARCH. DERMAT. & SYPH.]

AN INTERESTING CASE OF GUMMA OF THE LIVER IN EARLY INFANCY. FRANZ GERLÓCZY, Monatschr. f. Kinderh. **83**:357, 1940.

Gumma of the liver occurred in a child 20 months old without any positive serologic diagnosis—a rare occurrence in infants. In patients of this age diffuse

interstitial hepatitis occurs more often, while gummas occur more frequently in adults. Various differential diagnostic considerations could not quite explain this illness. Only postmortem and histologic examination were able to reveal its nature.

NEURATH, New York.

ROENTGEN DIAGNOSIS OF SYPHILITIC OSSEOUS CHANGES IN STILLBORN INFANTS AND IN INFANTS WHO DIED SOON AFTER BIRTH AS A METHOD OF DETECTING SYPHILIS IN THE MOTHERS. V. P. PANOV, Vestnik ven. i dermat., 1939, nos. 2 and 3, p. 86.

Twenty-five stillborn infants and 23 infants who died soon after birth were examined with roentgen rays for osseous changes. In 16 subjects specific changes were found; in 10 of these there were periostitis and osteochondritis. In 5 the changes were slight, suggestive only of osteochondritis. Of 8 macerated fetuses, 3 had distinct syphilitic changes in the bone, 1 had suggestive changes and 4 showed no changes. Of 16 subjects whose roentgenograms showed osseous changes, for only 4 was a diagnosis of syphilis made on the basis of these findings only.

The author considers the roentgenographic method of examining newborn children as valuable in detecting syphilis in mothers.

BLOOM, New York. [ARCH. DERMAT. & SYPH.]

ACTINOMYCOSIS OF THE INTERNAL ORGANS. G. I. PINCHUK, Vrach. delo (no. 9) **22**:614, 1940.

Three cases of internal actinomycosis in adults are reported. In the first case autopsy revealed actinomycosis of the third, fourth and fifth lumbar vertebrae. In the second case, in which also autopsy was done, there was an ileocecal actinomycosis with metastases to the left kidney and perinephric space, lungs, spleen and pleura. The third case was that of a young adult with pulmonary actinomycosis discovered on surgical drainage, who left the hospital unimproved. All 3 patients suffered from fever, general weakness and emaciation as well as localized pain and later swelling.

The author's conclusions are as follows: 1. Early diagnosis of actinomycosis of internal organs presents great difficulties. 2. Actinomycosis of the internal organs is accompanied with an elevation of temperature, frequently of the hectic type. The author believes that the febrile reaction is due not to a secondary infection but to the actinomycotic process itself. 3. The treatment of actinomycosis of the internal organs by roentgen rays and potassium iodide is not always effective.

BODER, Los Angeles.

SUDDEN DEATH CAUSED BY BRONCHIAL GLAND TUBERCULOSIS. ANDERS KRISTENSSON, Nord. med. **7**:1187 (July 6) 1940.

At the age of 4 months, a girl, born at full term, whose father suffered from pulmonary tuberculosis, fell ill with cough. She was first seen one month later. She was then dyspneic and somewhat cyanotic and had intense coughing, often in spasmodic attacks. There was no dulness. Harsh vesicular breathing and rhonchi were noted. There was splenomegaly. The temperature was subfebrile. The reaction to the Pirquet test was positive. The sedimentation rate was 28 mm. Roentgenograms showed a large infiltration of the right hilus and the right paratracheal space. The upper lobe of the right lung showed atelectasis. There was a somewhat enlarged hilar shadow on the left side. A fortnight later the child suddenly died from suffocation. The postmortem examination displayed a hazelnut-sized thrombus of caseous matter at the bifurcation of the trachea. The right wall of the trachea and of the right main bronchus was a little bulged into the lumen, and from this part a small perforation was leading into the caseous gland.

WALLGREN, Göteborg, Sweden.

CALMETTE VACCINATION OF CHILDREN IN TUBERCULOUS FAMILIES. HJÖRDIS LIND-CAMPBELL, Svenska läk.-tidning. **37**:1251 (July 26) 1940.

The author reports on 85 vaccinated, uninfected children belonging to tuberculous families, of whom 49 had been exposed to infection after the vaccination. The vaccinations had been made in the years 1933 to 1940. None of the children displayed any symptom or signs of tuberculous disease. A study of the occurrence of clinical tuberculosis in a similar group of unvaccinated children from a period before 1933 revealed that 14 per cent of the exposed children had acquired tuberculous disease and an additional 22 per cent had displayed abortive signs of tuberculosis.

WALLGREN, Göteborg, Sweden.

TWO EPIDEMICS OF TUBERCULOSIS AMONG SCHOOL CHILDREN. AXEL SASSE, Svenska läk.-tidning. **37**:1473 (Sept. 20) 1940.

In a country school a substitute teacher suffering from pulmonary tuberculosis infected most of the pupils, and 15 of them had to be sent to a hospital for treatment of primary pulmonary tuberculosis. In another country school another substitute teacher infected 11 children (50 per cent of his class), 3 of whom needed hospital treatment. In both cases the teacher ignored the illness previously, and in both groups of infected children the occurrence of erythema nodosum was the alarm signal that caused the physician to make a careful examination of the other children and the teachers and in that way to detect the source of infection.

WALLGREN, Göteborg, Sweden.

SIGNIFICANCE OF ERYTHEMA NODOSUM IN EPIDEMIOLOGY OF TUBERCULOSIS. P. BROUWER, Nederl. tijdschr. v. geneesk. **84**:1501 (April 20) 1940.

The author stresses the fact that erythema nodosum is frequently a symptom of a recently acquired infection with tuberculosis. On the basis of his experience with more than 100 cases observed between 1936 and 1939 in one province of Holland, he points to the great significance of this symptom, which often makes possible early diagnosis and treatment of tuberculosis; he illustrates his conception with some observations of his own.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels and Spleen

ROENTGENOLOGIC STUDIES OF THE SIZE OF THE HEART IN CHILDHOOD. H. B. TAUSSIG and M. GOLDENBERG, Am. Heart J. **21**:440 (April) 1941.

The authors studied changes in the size of the heart in children with rheumatic heart disease by superimposing teleroentgenograms. Three kinds of changes in the size of the heart were observed: (1) normal growth; (2) after a period of enlargement, no increase in size of the heart as the chest grew; (3) progressive enlargement.

Cardiac enlargement depended primarily not on the nature or extent of the valvular lesions, but on activity of rheumatic infection. The mortality rate was much higher in the group that showed progressive enlargement than in the other two groups.

GIBSON, Chicago.

A CASE OF BACTERIAL ENDOCARDITIS ILLUSTRATING THE MECHANISM OF LOCALIZATION AND THE NATURE OF VEGETATIONS. A. C. ALLEN, Am. Heart J. **21**:667 (May) 1941.

A case of bacterial endocarditis caused by Streptococcus viridans, in a heart with a large interventricular defect through which an aortic cusp had eventrated, with resulting pulmonic stenosis and aortic insufficiency, is reported.

The vegetations were localized to regurgitation pockets in the mural endocardium of the left ventricle, where there was constant impact by the regurgitant stream as a result of the aortic insufficiency.

The localization of vegetations at sites which are subjected to various hemodynamic forces is explained as the result of impact of, and contact with, the blood stream, and with bacteria circulating therein.

The histologic observations confirmed the theory previously advanced, namely that the vegetations of bacterial endocarditis are derived from necrotic valvular tissue, and the plasma and blood elements from eroded valvular blood vessels; this occurs after implantation of bacteria from blood within the chamber. This is contrary to the current concept that the vegetations are thrombi which are deposited on an inflamed endocardial surface as the blood flows past the valves.

AUTHOR'S SUMMARY.

LOCAL APPLICATION OF RUSSELL VIPER VENOM FOR CONTROL OF HEMORRHAGE. ROBERT C. PAGE and EDMOND G. THOMAS, M. Clin. North America **24**:777 (May) 1940.

Russell viper venom appears to accelerate greatly the action of thromboplastic substances, with which it acts synergistically. It appears to be capable of reactivating such substances that have become partially inactivated by heat, aging or chemical treatment. Hemorrhage, with the probable exception of that associated with prothrombin deficiency, may be effectively and promptly controlled by local application of a 1 : 10,000 solution of the venom.

In local bleeding occurring in hemophilic subjects a tough and elastic clot is produced by application of venom by means of saturated pledgets of cotton or by drops or spray. No harmful effects have been reported to follow proper administration of the venom.

A full review and discussion of the experimental and clinical evidence on which the therapeutic application of viper venom is based appear in the paper.

EUGENE SMITH, Ogden, Utah.

SOME RECENT ADVANCES IN THE TREATMENT OF HEMOPHILIA. THOMAS H. MCGAVACK, M. Clin. North America **24**:791 (May) 1940.

The development of measures effective in the control of bleeding in the hemophilic subject depends on a clearer understanding of the process of blood coagulation. This appears to be a biphasic reaction enzymic in character, concerned respectively with the formation of thrombin (thrombase) and fibrin. The present method of therapeutic approach is predicated on the apparently well formed conception that a deficiency exists in both plasma and tissue thromboplastins.

Several types of thromboplastic material, "globulin substance," have been prepared from animal and from human blood. Some of these may be of value as local applications, and those made from human blood may be given intravenously and intramuscularly. The amount of blood necessary for the preparation of the human material renders it commercially unavailable. Other disadvantages are that such a product is unstable and that repeated injections result in a refractory state or even in actual prolongation of the coagulation time. However, euglobulin substance of Lozner and Taylor appears to be free from these disadvantages.

Extracts of human placenta have been prepared, but those thus far produced show a wide variation in effective dosage and cumulative effects with reversal of action. They also have a tendency to produce intravascular clotting. Other thromboplastic substances of tissue origin have not as yet proved satisfactory.

The ability of certain snake venoms to transform prothrombin to thrombase has been proved. The most effective seems to be that of Russell's viper, local application of a solution of which is at times effective in the control of local bleeding.

McGavack's clinical experience in the use of an extract of shepherd's purse (koagamin) has been favorable. The clot-producing properties of this extract

appear to be due to its content of dicarboxylic acid. This substance may be used intravenously; it is stable and contains no protein. It would appear to be of value in the management of the actively bleeding patient.

EUGENE SMITH, Ogden, Utah.

USE OF PLASMA OR SERUM AS SUBSTITUTE FOR WHOLE BLOOD. C. H. BEST and D. Y. SOLANDT, Brit. M. J. **2**:116 (July 27) 1940.

The authors state that there is considerable uncertainty about the relative merits of serum and plasma as substitutes for whole blood in various clinics. They state that in their recent experimental work on animals serum and plasma have been used interchangeably and the results were identical. These materials are used both experimentally and clinically for two main purposes: first, to provide fluid and, secondly, to provide the serum proteins which by their osmotic pressure retain fluid in the blood stream or attract it from the tissues. They state that in so far as these two properties are concerned there is no significant difference between the serum and the plasma. They say it can now be safely stated that normal serum, concentrated serum and serum reconstituted after drying in a frozen state have been used in treatment in many clinical cases without the occurrence of any serious reaction. The main point they wish to bring out in their article is "that plasma and serum free from reaction-producing substances are physiologically and therapeutically identical and may be used interchangeably."

ROYSTER, University, Va.

EXTRATHORACIC ECTOPIA OF THE HEART: REPORT OF A CASE. SEVKET-SALIH-SOYSAL, Arch. de méd. d. enf. **43**:222 (July-Aug.) 1940.

Foy, in 1910, first discussed ectocardia and reported a case of its occurrence in a man of 37; later Torkomian observed an instance of this defect in a child of 3. The author describes a case in which it was observed in an infant of 4 months. The anomaly results from failure of the two divisions of the sternum to unite, this in turn permitting a hernia of the thoracic cage and extrusion of the heart.

In the case under consideration there was absence of the entire sternum except a small portion of the manubrium. The hiatus produced by the failure of both the gladiolus and the xiphoid process to develop permitted escape of abdominal viscera (the stomach and intestines) as well as of the heart. AMESSE, Denver.

INTRAPERICARDIAL AORTIC ANEURYSM IN A CHILD FOURTEEN YEARS OF AGE. R. B. ROSSI, Arch. argent. de pediat. **11**:175 (Feb.) 1940.

The author reports this very rare condition in a boy aged 14. Roentgenographic examinations showed an exceptionally large aorta and a pulsating aneurysm.

Syphilis was not a causative factor. At the time of admission to the hospital, the child showed active rheumatic symptoms. There was considerable precordial angina. Intensive treatment with sodium salicylate caused rapid improvement of the general condition and disappearance of the precordial pain.

The sedimentation rate of 55 mm. at the time of admission dropped to 16. The child apparently made a complete recovery. The aneurysm diminished in size. Considerable compensatory hypertrophy of the right ventricle developed.

SCHLUTZ, Chicago.

VALUE OF WELTMANN'S TEST IN CHILDHOOD. S. HOLIK, Arch. f. Kinderh. **118**:13 (Sept. 26) 1939.

Weltmann's test is based on the colloidal stability of the serum: Serum if sufficiently diluted with distilled water does not coagulate when heated, but it coagulates if a minimal amount of an electrolyte (the best is calcium chloride) is added. The normal concentration was found to be 0.05 per cent. No coagulation

or a coagulation in a strong concentration (0.07 to 0.08 per cent) is called a "shift to the left"; coagulation starting with a higher concentration (0.2 to 0.3 per cent) is called a "shift to the right."

The serums of 50 healthy children of various age groups were examined. No influence of the age of the children on the type of the reaction was observed. A "shift to the left" was found in cases of acute infection, of influenza, of pneumonia, of diphtheria, of sepsis and of meningitis. During convalescence this shift to the left changed to a shift to the right. A shift to the right was found in malaria, tetanus and icterus and in nearly all types of tuberculosis except exudative pleuritis.

ARON, Chicago.

ELECTROCARDIOGRAPHY DURING INFANCY: VII. THE ELECTROCARDIOGRAM IN CASES OF INFANTILE ECZEMA. A. NADRIA, Ztschr. f. Kinderh. **61**:659 (April 26) 1940.

Although the views regarding the cause of death in cases of eczema are widely divergent, it seems certain that circulatory failure plays a prominent role. The author's electrocardiographic observations on infants with eczema showed changes indicating myocardial damage or heightened vagal tone (more commonly the latter) in many cases. Changes may coincide with changes in the clinical picture.

SIEMSEN, Chicago.

ANEMIA OF THE PERNICIOUS TYPE IN A CHILD. P. SVASTITS, Orvosi hetil. **84**:179 (June 29) 1940.

A 13 year old girl with severe anemia and with the symptoms of blood regeneration was observed. Her condition improved quickly after injections of liver extract. The girl was sent home, but the same severe anemia developed twice within a year. It always improved after administration of liver extract. The clinical signs and the blood picture were typical of pernicious anemia, but it is well known that this anemia occurs rarely in children; therefore, Svastits calls the condition "anemia of pernicious type of unknown origin."

O. GÖTTCHE, Budapest, Hungary.

PATHOLOGY OF THROMBOPENIC PURPURA. T. MASUZAWA, Acta pædiat. japon. **46**:1485 (Dec. 20) 1940.

Masuzawa reports 3 cases of thrombopenic purpura, 2 in which the disease was chronic and 1 in which it was acute. In none of the patients was it possible to trace the decreased platelet count to any definite cause. The hemorrhagic manifestation was chiefly that of bleeding into the skin, epistaxis and gingival hemorrhage. In all these cases the lymph nodes were but slightly enlarged, the liver was practically normal in size and the spleen was not palpable. Except for transient fever following blood transfusions, the course of the disease was entirely afebrile. The blood pictures were typical of thrombopenic purpura, with a symmetric diminution in red cell count and hemoglobin values. In only 1 was there a tendency to leukopenia (lymphocytopenia), the white cell count being normal in the other 2. In all the cases the bleeding time was prolonged, but the coagulation time was either normal or only slightly delayed. In 2 cases a systolic murmur was heard over the apex; but in the third the heart sound remained clear throughout. In 1 case cerebral symptoms developed and death ensued. Pathologically, the bone marrow was hyperplastic in 2 cases, but in the third there was some evidence of atrophy. In 1 instance only was the spleen enlarged, with evidence of increased platelet destruction. In 1 case the lymphoid tissue exhibited generalized hyperplasia, suggesting status lymphaticus. Histologically, in only 1 instance was there an increased number of megakaryocytes in the bone marrow, these cells being practically absent in the other 2 cases. In the former case the increased platelet destruction, as evidenced by the enlarged spleen, apparently

caused the increase in megakaryocytes in the bone marrow. In the 2 cases with no evidence of increased platelet destruction the marrow megakaryocytes that were present showed hyperplasia.

KATO, Chicago.

INFLUENCE OF HESPERIDINE ON ERYTHROCYTE SEDIMENTATION RATE. K. YOSHIDA, Acta pædiat. japon. **46**:1531 (Dec. 20) 1940.

Assuming that vitamin P exerts an inhibitory effect on the permeability of capillaries, Yoshida endeavored to determine the effect of this vitamin on the erythrocyte sedimentation in various diseases of children. By either oral administration or subcutaneous injection, it definitely decreased the rate of erythrocyte sedimentation in all instances, a fact which indicates a beneficial effect of vitamin P on the disease process.

KATO, Chicago.

CASE OF ECTOPIA CORDIS IN A LIVING CHILD, BORN AT TERM. POUL KÜHNEL, Acta obst. et gynec. Scandinav. **20**:128, 1940.

In the case reported here, the infant exhibited an abdominothoracic defect through which the heart, uncovered by pericardium, protruded. A small band of amnion extended from the heart to the amniotic sac. No abdominal organs were extruded, and the abdominal defect was covered by a thin membrane composed of amnion and peritoneum. The heart continued to beat for twenty-six hours after birth.

POTTER, Chicago.

EFFECT OF HESPERIDINE ON THE BLOOD PICTURE OF CHILDREN. K. YOSHIDA, Acta pædiat. japon. **46**:1516 (Dec. 20) 1940.

Yoshida administered vitamin P in the form of hesperidine in infants and young children and studied the changes that ensued in the blood picture. A 2.5 per cent solution of hesperidine was injected subcutaneously in doses varying from 1 to 4 cc., and the results obtained from a single injection were compared with those obtained from repeated daily injections. He found that hesperidine had no influence on the red cell count or on hemoglobin values, but there was a decided reticulocyte response. This was apparently due to the appearance of young erythrocytes in the circulation as a result of mobilization, rather than of increased formation, since no change was observed in the levels of cell count or hemoglobin. The blood platelets increased temporarily following a single injection but returned to the original level within twenty-four hours; repeated daily injections had no subsequent effect on the platelet count. The leukocyte count was also definitely elevated, due chiefly to the absolute increase in the neutrophilic granulocytes, since other cell types showed no changes whatever.

KATO, Chicago.

PHYSICOCHEMICAL PROPERTIES OF HUMAN BLOOD: I. VOLUME OF CELLS. YOSITAKA UEHARA, Keizyô J. Med. **10**:135 (Feb.) 1940.

The author emphasizes the importance of maintaining fixed conditions in any comparative study of blood cell volume using hematocrit readings. For example, the height of the blood column and the force of the centrifuge must always be the same.

In his study he found that the volume of red cells in citrated blood was 34.56 ± 2.57 per cent for males (121 cases) and 32.03 ± 2.89 per cent for females (64 cases). In noncitrated blood, the value for males was 43.21 ± 3.30 per cent and for females 39.94 ± 3.45 per cent. The volume of white cells in citrated blood was 0.64 ± 0.20 per cent for males and 0.60 ± 0.21 per cent for females. In noncitrated blood it was 0.79 ± 0.20 per cent for males and 0.77 ± 0.23 per cent for females.

LESLIE, Evanston, Ill.

CONSTITUTIONAL ANEMIA IN TWO CHILDREN. PALLE HJORT, Nord. med. **7**:1313 (Aug. 3) 1940.

Hjort describes 2 cases of severe, fatal anemia with leukopenia and thrombopenia in a brother and sister 8 years of age. The boy suffered from clubfoot and the girl from congenital luxation of the hip. For two and a half and four years respectively these children were kept alive by repeated (thirty) blood transfusions, all other treatment being without effect. Autopsy of the boy revealed hemorrhages in almost all internal organs, pigmentation and melanosis, atrophy of the thymus gland and the testes, and hypoplastic bone marrow. Similar changes were noted in the girl. Examination of the family history disclosed a pronounced disposition to congenital osseous malformations on the maternal side. These 2 cases are compared with 5 cases previously described by Fanconi (*Jahrb. f. Kinderh.* **117**: 257, 1927), Uhlinger (*Klin. Wchnschr.* **8**:150, 1929) and van Leeuwen (*Folia haemat.* **49**:434, 1933) in which children aged from 6 to 9 years showed anemia, leukopenia and thrombopenia and in addition various congenital morphologic anomalies.

WALLGREN, Göteborg, Sweden.

METHOD OF DETERMINATION OF THE PROTHROMBIN CONTENT IN 0.1 TO 0.2 CC. OF CAPILLARY BLOOD. P. PLUM and H. DAM, Ugesk. f. læger **102**:946 (Sept. 12) 1940.

Clotting of the blood is prevented by mixing the blood with a solution of heparin. The technic and the errors of the method are discussed. In double determinations the values corresponded well (10 per cent errors).

WALLGREN, Göteborg, Sweden.

CONGENITAL ARTERIOVENOUS FISTULA. P. FORMYNE, Nederl. tijdschr. v. geneesk. **84**:1487 (April 20) 1940.

The author describes a case of arteriovenous fistula in the left fifth finger of a woman 23 years old, combined with a separate congenital arterial aneurysm in the left hand. Pronounced differences were noted in the oxygen saturation of the blood in different veins of the same (left) arm. Roentgen examination demonstrated increased length of a phalanx in the affected finger, with intraossal dilatation of Havers' blood vessels.

The need for a careful clinical, roentgenologic and anatomic study of the group of so-called vascular tumors is emphasized.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF CONGENITAL INSUFFICIENCY OF THE PULMONARY ARTERY. S. TILLEMA and E. VAN DER KUIP, Nederl. tijdschr. v. geneesk. **84**:2450 (June 29) 1940.

In a Javanese woman who had lived at Paramaribo (Netherlands West Indies), who had suffered from atrophic hepatic cirrhosis, syphilis and gonorrheal cervicitis, autopsy showed the anterior semilunar valve of the pulmonary artery to be lacking. The patient had never had any trouble from dyspnea or shortness of breath.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Nose, Throat and Ear

MASTOIDITIS IN INFANCY. J. C. OREGGIA, Arch. de pediat. d. Uruguay **10**:585 (Oct.) 1939.

The author describes three types of mastoiditis occurring in infancy: (1) simple, (2) complex and (3) occult. The one of most interest to the pediatrician is the third type, which results from obscure fever in the absence of all other physical findings. This type is found particularly in malnourished children and commonly develops into a mucopurulent osteitis. The diagnosis can often be made by roentgen examination.

SCHLUTZ, Chicago.

VALUE OF DIRECT LARYNGOSCOPY FOR TYPING PNEUMOCOCCI IN CHILDREN. J. CLAUSEN and BØRGE VAMMEN, Nord. med. **5**:5 (Jan. 6) 1940.

In 18 of 22 healthy children saprophytic pneumococci were demonstrated by the usual throat swabs, while in only 10 healthy children were they revealed by swabbing through the laryngoscope. In 23 of 26 children suffering from acute pneumonia, pneumococci were demonstrated. In 19 cases the results were identical with the two methods of swabbing, and in 3 cases swabbing through the laryngoscope rendered the more reliable result.

WALLGREN, Göteborg, Sweden.

FATAL CASE OF OSTEOMYELITIS OF BASE OF SKULL FOLLOWING ADENOIDECTOMY. T. KRARUP, Nord. med. **7**:1613 (Sept. 27) 1940.

A girl of 6 years had undergone adenoidectomy during an unnoticed acute otitis media. High fever developed after the operation. She was first seen six days later. There were no meningitic signs. Purulent otitis media was present on the right side, with mastoiditis, for which an operation was performed. Three days after her admission to the hospital there was pleocytosis of the spinal fluid, which contained hemolytic streptococci. The child died thirteen days after the adenoidectomy. The postmortem examination revealed an osteitic process of the ethmoid and sphenoid bones.

WALLGREN, Göteborg, Sweden.

Diseases of Lungs, Pleura and Mediastinum

AN EVALUATION OF THE COMBINED EFFECTS OF SULFAPYRIDINE AND THE BARBITURATES IN THE TREATMENT OF PNEUMONIA. WILLIAM KING and HERMAN J. MOERSCH, J. Lab. & Clin. Med. **26**:793 (Feb.) 1941.

Because of a report by Adriani in 1939 that rats under treatment with sulfanilamide were rendered highly susceptible to the action of certain barbiturates, the authors undertook a study of patients who had received sulfapyridine. The patients whose cases they studied had lobar pneumonia and bronchopneumonia, and all had been given one or more sedative doses of a barbiturate. The authors conclude that in ordinary sedative doses barbiturates may be used with apparent immunity for patients receiving sulfapyridine or sulfanilamide.

GARD, Galveston, Texas.

THE TREATMENT OF LOBAR PNEUMONIA WITH SULFATHIAZOLE AND SULFAPYRIDINE. MORGAN CUTTS, ALEX M. BURGESS and FRANCIS H. CHAFEE, New England J. Med. **223**:762 (Nov. 7) 1940.

The study deals with 60 patients with lobar pneumonia. Alternate patients received sulfapyridine and sulfathiazole. The diagnosis was confirmed by roentgen examination in all cases. In 80 per cent of the cases there were typable pneumococci.

The mortality was 10 per cent in each group. It was found that a prompter fall in temperature occurred in patients treated with sulfapyridine. However, at the end of forty-eight hours approximately the same number were afebrile in the two groups.

One difference immediately apparent is the decreased tendency to nausea and vomiting seen with sulfathiazole (30 per cent) as compared with sulfapyridine (60 per cent)).

GENGENBACH, Denver.

OTITIS MEDIA AND LOBAR PNEUMONIA IN YOUNG CHILDREN. M. KRASSNIG, Monatschr. f. Ohrenh. **74**:349 (July) 1940.

When in infants with otitis no improvement is achieved after paracentesis, a central pneumonia must be suspected. Drainage from the ear will be poor until the pneumonia has resolved. Then only will the ear drain freely and the disease

take its normal course. The opinion is ventured that the aural symptoms are metastatic by way of the blood stream, the primary focus being the pneumonia, which is recognized only after a few days.

LEDERER, Chicago. [ARCH. OTOLARYNG.]

THERAPEUTIC RESULTS OF SULFAPYRIDINE IN EMPYEMA OF CHILDREN. H. MURASE, Acta pædiat. japon. **46**:1383 (Nov. 20) 1940.

The author reports the therapeutic results of sulfapyridine in 16 cases of empyema in children, 10 of which were in infants under 2 years of age. Positive cultures for Diplococcus pneumoniae were obtained in 10 of these cases, while in 1 both pneumococci and hemolytic streptococci were isolated. In 6 cases the clinical condition of the patient greatly improved after institution of the treatment, as evidenced by a drop in fever, diminution in the pleural exudate and leukopenia. In 3 instances no apparent improvement was noted, and in these cases alone there was a tendency toward leukocytosis instead of leukopenia. Two infants, 3 months and 7 months of age respectively, died of complicating meningitis; administration of sulfapyridine affected these 2 in no way.

KATO, Chicago.

PULMONARY ABSCESS. S. VAN CREVELD, Nederl. tijdschr. v. geneesk. **84**:590 (Feb. 17) 1940.

In this clinical lecture, causation, course and modern aspects of treatment of pulmonary abscess in childhood are discussed. As an example is given the case of a girl 7 years old in whom a large pulmonary abscess developed after tonsillectomy with an interval of eight months of perfect health between the operation and the appearance of symptoms of the abscess. Clubbed fingers developed during the illness and disappeared later, when the abscess had been coughed up after a long illness.

AUTHOR'S ABSTRACT.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

A COMPARISON OF THE INHIBITORY ACTION OF DIFFERENT FATS AND FATTY ACIDS INTRODUCED INTO THE DUODENUM ON GASTRIC CONTRACTIONS. W. I. CARD, Am. J. Digest. Dis. **8**:47 (Feb.) 1941.

These experiments were performed on 2 patients with mild epilepsy who had less than one seizure a month. After a twelve hour fasting period, a duodenal tube was passed into the stomach and its contents aspirated. The tube was then allowed to pass on into the duodenum, a fluoroscopic examination being made if any doubt as to its position occurred. Then the patient sat up and swallowed a tube with a balloon on its end. This was connected to a bromoform recorder, and the balloon was inflated with from 150 to 200 cc. of air, according to the size of the patient. The degree of inflation remained constant with any one patient.

No evidence was obtained in the case of the pure fats tested that a significant difference exists in their action.

Fatty acids were far more effective than their corresponding fats in inhibiting gastric contraction, and a linear relation was demonstrated between the dose of fatty acid used and the mean duration of inhibition obtained.

MORRISON, Savannah, Ga.

A FURTHER STUDY OF THE EFFECT OF VARIOUS ANTACIDS ON THE HYDROGEN-ION CONCENTRATION OF THE GASTRIC CONTENTS. JOSEPH B. KIRSNER, Am. J. Digest. Dis. **8**:53 (Feb.) 1941.

Five antacids were investigated for their neutralizing effects in 98 experiments performed on 9 patients with healing duodenal ulcer. The hydrogen ion concentration of the gastric contents removed hourly was determined by the glass

electrode method. The alkalis were administered hourly, halfway between aspirations of the gastric contents. The alkalis used included magnesium trisilicate, tribasic calcium phosphate, tribasic magnesium phosphate, a mixture (tablet) of calcium carbonate, magnesium carbonate and white sugar, and magnesium carbonate.

The author found that magnesium carbonate in 2 Gm. doses hourly is a highly effective neutralizer of gastric acidity. The mixture of calcium carbonate and magnesium carbonate also greatly reduces gastric acidity. Tribasic magnesium phosphate, tribasic calcium phosphate and magnesium trisilicate are progressively less effective, in the order named, in maintaining adequate neutralization.

MORRISON, Savannah, Ga.

ON THE FATE OF INGESTED PECTIN. S. C. WERCH and A. C. IVY, Am. J. Digest. Dis. **8**:101 (April) 1941.

Experiments were carried out on both dogs and human beings. In the dog, an average of 90 per cent of the pectin was decomposed when pectin was fed with a mixed diet, and 50 per cent was decomposed when the pectin was fed during fasting. Decomposition of the pectin fed during fasting depended on the rate of passage through the gastrointestinal tract, for in the dogs which defecated frequently the recovery of pectin from the feces ranged from about 75 to 96 per cent, while in the dogs which defecated but once during the absorption period the recovery ranged from 2 to 30 per cent. This tends to show that decomposition may be furthered if the pectin fed is retained for longer periods. The results also indicate that the decomposition is carried further when pectin is added to a mixed diet than when given alone. The results obtained with human beings, when similar quantities of pectin were given with a mixed diet, did not differ from those of the dog, for here, too, decomposition of about 90 per cent took place. However, when pectin was fed alone, the recovery from human feces averaged less than in the dog, indicating that a fasting man is capable of decomposing more pectin than a fasting dog.

Ileostomy experiments showed both in the human being and in the dog that breakdown occurs chiefly in the colon and not in the upper part of the intestine and that bacterial enzymes are involved rather than the enzymes of the animal organism.

MORRISON, Savannah, Ga.

THE EFFECT OF FEEDING APPLE SAUCE ON INDUCED DIARRHEA IN RATS. Z. I. KERTESZ, MARTHA S. WALKER and C. M. MCCAY, Am. J. Digest. Dis. **8**:124 (April) 1941.

The authors induced diarrhea in rats by the daily feeding of a diet of 10 cc. of milk containing 1 Gm. of lactose and maintained the diarrhea for several days. They used rats 3 weeks old, which would correspond, on the basis of life span, to children about 2 years of age.

When apple sauce was fed to the rats after the diarrhea had persisted for three days, most of the animals were cured. The efficiency of the apple sauce in curing the diarrhea was rated at 84 per cent. (The percentage was based on 100 per cent for cured, 50 per cent for improved, and no per cent for unimproved. Hence, if 10 rats were fed and 8 were cured, 1 improved and 1 unimproved, the efficiency would be 85 per cent.)

Apple sauce in which the pectins were digested by enzymes showed an efficiency of 39 per cent, indicating the important role of pectins in the therapeutic action.

The residue which was obtained after digestion by the enzyme and exhaustive extraction of the apple sauce by water and which contained almost exclusively "crude fiber" showed definite curative action, indicating that materials other than the pectins also contributed to the curative action of the apple sauce. Components of apple sauce extracted by water and precipitated by alcohol had an efficiency of 23 per cent, and the residue after extraction, when fed to rats, had an efficiency of 53 per cent.

This experimental study indicates that the curative effect of the apple sauce depended on the pectins and fibrous materials. There was no indication that the presence of uronic acids had any role in curing the induced diarrhea in rats.

[ABSTRACTER'S NOTE: It should be remembered that this is a nutritional type of diarrhea that has been induced. Whether the same results may be obtained in an infectious type of diarrhea is yet to be shown.] MORRISON, Savannah, Ga.

THE CONGENITAL ABSENCE OF GALL BLADDER. P. J. SARMA, Am. J. Digest. Dis. **8**:139 (April) 1941.

Four cases of congenital absence of the gallbladder are reported. Three of these patients had dilatation of the common bile duct and stones. These 3 patients showed no recurrence of symptoms when the common bile duct was opened and the stones removed. The fourth patient had had two previous operations, at neither of which a gallbladder was found. Dr. Hedblom also failed to find a gallbladder at the third operation on this patient.

Two points are stressed: (1) that anatomic anomalies of the biliary tract are common and (2) that careful exploration is necessary.

MORRISON, Savannah, Ga.

A REËXAMINATION OF THE RÔLE OF THE STOMACH IN THE DIGESTION OF CARBOHYDRATE AND PROTEIN. J. M. BEAZELL, Am. J. Physiol. **132**:42 (Feb.) 1941.

Using young normal male adults as subjects, the relative importance of the human stomach in the digestion of protein and starch has been investigated. The experiment consisted of feeding the subjects a meal of known composition, removing it from the stomach at the end of a specified period of time, and determining the ratio of "digested" to "undigested" protein and starch in the material recovered from the stomach. The production of reducing sugars in the case of starch and the production of nitrogenous material soluble in 2.5 per cent tungstic acid in the case of protein were arbitrarily selected as end points of digestion.

In 4 experiments in which the test meal corresponded with what might be considered an "average" meal, samples for analysis were obtained by having the subjects empty the stomach as completely as possible by voluntary regurgitation at the end of either one-half or one hour. Under these circumstances it was found that, irrespective of the time that the meal remained in the stomach, approximately 40 per cent of the remaining carbohydrate was in the form of reducing sugars, while essentially none of the protein had been reduced to a form soluble in tungstic acid.

In 13 experiments in which a finely divided meal was used, the stomach was completely evacuated at the end of either one or two hours by means of an Ewald tube. Under these circumstances it was found that of the material remaining in the stomach at the end of one hour, an average of 19.6 per cent of the starch was in the form of reducing sugars while only 2.45 per cent of the nitrogen was soluble in tungstic acid. When the digestion period was extended to two hours, 9.5 per cent of the nitrogen remaining in the stomach was in a "digested" form.

In view of these observations it is felt that the conventional concept that the stomach plays an unimportant role in the digestion of starch and an important role in the digestion of protein is open to revision. AUTHOR'S SUMMARY.

THE ABSORPTION OF CAROTENE FROM ISOLATED INTESTINAL LOOPS. J. LOGAN IRVIN, JOSEPH KIPALA and CHARLES G. JOHNSTON, Am. J. Physiol. **132**:202 (Feb.) 1941.

The absorption of carotene from isolated intestinal loops of dogs has been studied by means of photoelectric colorimetric determination of the provitamin in the loop contents before and after absorption periods. Carotene is not absorbed in an analytically significant amount when placed in the loops in concentrated

solutions in cottonseed oil without bile and pancreatic lipase. When carotene solutions are given along with hog or ox gallbladder bile, significant amounts are absorbed. Similarly, small amounts are absorbed when carotene in oil is introduced into the loops with pancreatic lipase. However, when the carotene solution is placed in the intestinal loops with both bile and pancreatic lipase, much larger amounts are absorbed.

Pure bile salts are capable of promoting the absorption of carotene. Sodium desoxycholate is the most effective bile salt of those studied, but sodium cholate and sodium glycocholate are also effective. These results and other evidence in the literature suggest that the choleate theory of the mechanism for the absorption of carotene should be minimized but not abandoned completely.

In the presence of identical amounts of bile and lipase, the rate of absorption of carotene is greater when the initial amount of carotene in the loop is increased. Reports on the inhibiting effect of mineral oil on the absorption of carotene are confirmed.

AUTHORS' SUMMARY.

THE INHIBITION OF GASTRIC SECRETION BY THE INTRAVENOUS INJECTION OF CALCIUM SALTS. RHODA GRANT, Am. J. Physiol. **132**:460 (March) 1941.

The essential interest in this problem lies in the hypothesis, for which clinical and physiologic evidence exists, that the parathyroid glands in some way at present not understood influence the function of the gastric glands. In acute experiments on dogs injection of calcium lactate or of calcium chloride inhibits both the nervous and the chemical type of secretion. The inhibitory agent appears to be the calcium radical. The degree of inhibition depends to some extent on the degree of hypercalcemia. The mechanism of inhibition has not been found.

JOHN D. NOURSE, Cleveland.

SYMPTOMS OF GASTROINTESTINAL ORIGIN IN THE EAR, NOSE AND THROAT. WILLIAM LAWRENCE GATEWOOD, Arch. Otolaryng. **33**:592 (April) 1941.

The author directs attention to the frequency with which gastrointestinal allergy is manifested in the ears, nose and throat. By setting up a toxic condition in the lower part of the bowel, it causes this region to become a reservoir for infection, which is subsequently conveyed by the lymphatic and vascular systems to distant parts of the body. When a complete otorhinolaryngologic check-up fails to reveal a pathologic condition, a thorough investigation of the patient's dietary habits is advocated. Illustrative cases are presented.

GREENWOOD, Chicago.

OXYURIASIS OF THE APPENDIX; A CLINICAL STUDY OF 31 CASES. ROBERT W. HILLMAN, Brooklyn Hosp. J. **3**:83 (April) 1941.

In a four year period at the Brooklyn Hospital, among 1,294 cases of suspected appendicitis, Oxyuris vermicularis was found in the appendix in 2.39 per cent. It was most frequent in girls of school age and adolescence. The history is usually that of recurrent attacks over a period of one to two years, a complaint of mild abdominal pain, nausea and sometimes vomiting for several days before admission. The patients do not appear acutely ill; they have a normal temperature but slightly elevated white blood cell count, with an increase in the polymorphonuclear percentage. Except for the presence of the organism in the lumen of the appendix, there is no characteristic pathologic picture; there is usually entire absence of inflammatory changes.

LESLIE, Evanston, Ill.

THE EFFECT OF CITRUS JUICES AND VARIOUS MOUTH PROPHYLAXES ON THE ORAL FLORA AND SALIVA. H. J. FLORESTANO, MYRON A. ELLIOTT and J. E. FABER JR., J. Bact. **41**:605 (May) 1941.

This is a most interesting study in that it was shown that the most effective agents in actual removal of micro-organisms from the mouth were two commer-

cial dentifrices, one containing sodium ricinoleate and the other sodium alkyl sulfate. However, the authors found that during a two hour interval after prophylaxis these agents showed the smallest percentage inhibition of growth of the remaining bacteria when compared with the other materials tested. The materials producing the greatest inhibition of growth were the citrus fruit juices.

STOESSER, Minneapolis, Minn.

PEPTIC ULCER IN CHILDREN: REPORT OF TEN CASES. WILLIAM F. BURDICK, J. Pediat. **17**:654 (Nov.) 1940.

A survey of 21,231 admissions to the Children's Hospital in Washington, D. C., revealed 8 cases of peptic ulcer (6 of duodenal and 2 of gastric). Positive fluoroscopic and roentgenographic evidence was obtained in 5 cases. In 2 cases the diagnosis was made at autopsy; in the remaining case only a clinical diagnosis was made. Reports of these 8 cases and of 2 cases seen in private practice are presented.

RAUH, Cincinnati.

INVESTIGATIONS OF BLOOD CHLORIDES IN SEVERE DIGESTIVE DISTURBANCES IN INFANCY: THERAPEUTIC INDICATIONS SUGGESTED BY THE STUDIES. P. ROHMER and E. SCHNEEGANS, Bull. Soc. pédiat. de Paris **37**:150 (March) 1939.

When the concentration of blood chlorides is low or normal, as well as in the majority of cases in which it is increased, restoration of proper water balance may be secured by the administration of physiologic solution of sodium chloride orally, subcutaneously or intravenously. The good results obtained may be explained by the fact that there is usually a negative balance of sodium chloride which is masked by the blood concentration due to dehydration. In 15 cases in which an increase in the ratio of corpuscular to plasma chlorides was present the use of Ringer's solution gave good results. Proper renal function, which is restored as soon as adequate water and electrolytes are furnished, takes care of necessary excretion. Physiologic solution of sodium chlorides is always tolerated for the first day. Its prolonged administration may do harm if diuresis and excretion of chlorides do not take place; absence of such excretion is, however, exceptional. Dextrose solution is not recommended, since it tends to decrease the concentration of chlorides in the blood and to increase dehydration by stimulating diuresis.

BENJAMIN, Montreal, Canada.

IS THERE A RELATION BETWEEN DEHYDRATION, URINARY CASTS AND ALBUMINURIA IN DYSPEPSIA IN INFANCY? E. SCHNEEGANS, Bull. Soc. pédiat. de Paris **37**:160 (March) 1939.

Urinary casts occur frequently in infants manifesting digestive disturbances and dehydration. They are possibly related to the dehydration and not necessarily to the digestive alteration.

BENJAMIN, Montreal, Canada.

SIALADENITIS IN A PREMATURE INFANT. SANTOS L. CRESPI, An. Soc. puericult. Buenos Aires **7**:6 (Jan.-March) 1940.

An infant born one month prematurely on May 23, 1940, was brought to the clinic on June 26, 1940 because the mother noted restlessness and a swelling in the left submaxillary region, which was increasing in size. The child's temperature was 39 C. (102.2 F.). In the submaxillary region there was a swelling, the size of a nut, covered by red and vascularized skin. Palpation elicited pain, and there was fluctuation. When a compression was made in the swelling, pus exuded from the left Wharton's duct. Culture showed staphylococci. The next day an incision was made and pus was evacuated. In six days the wound was healed. Three days later, the infant had an attack of grip with bronchopneumonia. Sulfapyridine, 0.5 Gm. in twenty-four hours, was given as well as expectorants and cardiac stimulants. In September the child was completely well, and the weight was 5,400 Gm.

GIFFEN, Toledo, Ohio.

BILIARY LITHIASIS IN CHILDHOOD. H. J. NOTTI, H. FERRER and A. GRINFELD, Arch. argent. de pediat. **11**:167 (Feb.) 1940.

The authors state that in the province of Mendoza, Argentina, numerous children have biliary lithiasis. They believe this is due to the large number of gastrointestinal disorders which occur during childhood in this province. The water in this province contains a very high percentage of various salts. The authors are of the opinion that this condition would favor the development of biliary calculi, and they believe that it was possibly the cause in the cases they report. The condition occurred in a child aged 10 years. A cholecystotomy was performed with excellent results, and the child made a complete recovery. SCHLUTZ, Chicago.

PRIMARY STREPTOCOCCIC PERITONITIS SUCCESSFULLY TREATED WITH SULFAPYRIDINE. TORSTEIN DALE, Nord. med. **5**:98 (Jan. 20) 1940.

A girl of 4 years fell ill with diarrhea, vomiting and abdominal pains localized especially on the right side. She was first seen two days later, at which time her condition was serious, with clinical signs of acute peritonitis. At operation a diffuse peritonitis with a seropurulent liquid containing hemolytic streptococci was found. The extirpated appendix was normal. After treatment with sulfapyridine the child made a rapid recovery. WALLGREN, Göteborg, Sweden.

PLASMA PHOSPHATASE IN HEPATITIS. M. VERMEHREN, Nord. med. **6**:923 (May 18) 1940.

Determination of the amount of phosphatase in the plasma is of no value in the differentiation between jaundice of toxi-infectious origin and jaundice due to a benign obstruction. As a means of differentiation of hepatitis from malignant obstruction the determination of phosphatase activity may be of importance.

WALLGREN, Göteborg, Sweden.

BIOPSY OF THE LIVER IN CATARRHAL JAUNDICE. K. ROHOLM and T. IVERSEN, Ugesk. f. læger **102**:42 (Jan. 11) 1940.

Biopsy of the liver by means of a puncture syringe method was carried out on 17 patients suffering from catarrhal jaundice between the third and the forty-eighth day after the appearance of the jaundice. In all cases there were distinct pathologic changes of the hepatic parenchyma of an infectious and degenerative type, with variable tendency to proliferation of connective tissue.

WALLGREN, Göteborg, Sweden.

BENZIDINE TEST ON BLOOD IN THE STOOLS OF INFANTS. KAI STAGGEMEIER, Ugesk. f. læger **102**:244 (March 14) 1940.

Four hundred and twenty-one stools from 91 infants were tested (subjects who had had blood mixed with the milk or who had diseases producing bleeding from the digestive tract or obvious bloody stools were excluded). A positive reaction was found in 49.9 per cent of the samples. At least one positive reaction occurred in 70.3 per cent of the children, mostly premature babies. There was no evidence of hypovitaminosis C. WALLGREN, Göteborg, Sweden.

SYMPTOMATOLOGY AND TREATMENT OF FOREIGN BODIES IN THE ESOPHAGUS. E. HUIZINGA, Nederl. tijdschr. v. geneesk. **84**:797 (March 2) 1940.

All of the 125 patients with foreign bodies in their esophagi who have been treated by the author since 1924 have been cured. For only 6 was operation necessary. The value of Minnegerodes sign, detection of air between the trachea and the vertebral column by roentgen examination, is discussed. There are three possibilities: (1) a small air bubble in the esophagus, (2) a large air bubble, most

often in a periesophageal abscess, and (3) interstitial emphysema, by which a perforation is proved with certainty.

In case of perforation, at first expectant treatment is permitted, but signs of inflammation make surgical intervention necessary. Esophagotomy is required only when removal of the foreign body by endoscopy seems too risky or when attempts at removal fail. When perforation and inflammation by a foreign body have occurred, first of all the esophagus must be exposed, after which one must determine by which route the object can be removed with the least risk.

VAN CREVELD, Amsterdam, Netherlands.

ENDOPHLEBITIS HEPATICA OBLITERANS. P. FORMYNE, Nederl. tijdschr. v. geneesk. **84**:932 (March 9) 1940.

Formyne describes a case of endophlebitis hepatica obliterans with clinical diagnosis and autopsy verification. He discusses the clinical symptoms in comparison with the experiments of Mann on total extirpation of the liver and considers the macroscopic and microscopic anatomic observations. He describes a second case in which the diagnosis was made at autopsy. The different theories on causation found in the literature are discussed. All of them seem to be untenable at present, and the conclusion is drawn that the cause is not yet known.

VAN CREVELD, Amsterdam, Netherlands.

Nervous Diseases

LIPOBLASTIC MENINGIOMA. W. TRACY HAVERFIELD and A. EARL WALKER, Arch. Surg. **42**:371 (Feb.) 1941.

A girl of 8 years was admitted to the hospital with a history of transient attacks of aphasia and twitching of the right side of the face. A diagnosis of epilepsy was made, and the patient was discharged. Encephalograms taken later revealed no definite abnormality. In 1939, at the age of 12 years, the child complained for the first time of headaches and blurred vision. Neurologic examination showed a somewhat irritable child who complained of headache and visual impairment. There were hyperactive reflexes in the right arm and leg and a choked disk of 2 to 3 D. Electroencephalograms showed abnormal waves from the left frontal region, and a ventriculogram confirmed the presence of a space-taking lesion in the left frontoparietal area. An osteoplastic craniotomy was performed, exposing a large, soft, yellowish, friable tumor. In the posterior part of the field the dura was intact, but anteriorly it was absent, the tumor completely replacing it. The inner table of the frontal bone was roughened, owing to invasion and erosion by the tumor. Sharp bleeding during reflection of the bone flap caused the operator to satisfy himself with removal of sufficient tumor to replace the flap and then to close the wound. Subsequently, roentgen radiation was administered to reduce the vascularity of the growth, and later two surgical procedures were necessary before removal was accomplished. The child recovered, with marked right hemiparesis, astereognosis and sensory speech defect.

Grossly, the specimens before fixation had a marked yellow color. Microscopically, all gradations from spindle cells with small vacuoles to large ballooned cells resembling adult fat cells were seen in certain areas of the tumor. The general cellular structure—sheets of meningotheliomatous cells and the arrangement of the cells in whorls and palisades—justifies the diagnosis of meningioma. Practically every cell in the tumor contained fat granules, although areas of frank degeneration were rare. The authors believe that the intracellular fat was the product of the peculiar functional activity of the mesenchymal cells from which the tumor developed. They have been unable to find the report of a similar tumor in the literature.

GRANT, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

EQUINE ENCEPHALITIS IN THE SAN JOAQUIN VALLEY. R. J. VAN WAGENEN, California & West. Med. **54**:264 (May) 1941.

The author gives a clinical report of 15 cases of equine encephalitis observed during the epidemic of 1937-1938. It is felt that we are not dealing with a new disease, but rather are just beginning to recognize in human beings a condition which has been reported in horses as far back as 1847. Because of the lack of a history of exposure to horses in most cases, there must be a vector involved in the transmission of the disease; the mosquito has been suggested but not proved in this respect. All 15 patients in this report were males, and their ages varied from 20 months to 66 years. In general, the young adult age group prevailed. There were 12 complete recoveries, 1 patient had rather marked residual symptoms and 2 patients died. No instance of a cross infection among human beings has been reported. There is no specific therapy.

DAVIS, San Francisco.

IDENTIFICATION OF THE VIRUS OF LYMPHOCYTIC CHORIOMENINGITIS. J. E. SMADEL and M. J. WALL, J. Bact. **41**:421 (April) 1941.

The authors feel that a relatively simple and rapid method of identifying the virus of lymphocytic choriomeningitis is of importance not only for special workers in the virus field but for persons called on in a routine manner to isolate and identify etiologic agents of human diseases. The identification of the virus by cross immunity and neutralization tests is expensive and time consuming. Therefore, complement fixation may offer the most satisfactory method. The authors found that it offered an adequate, simple and inexpensive procedure for the identification of the virus of lymphocytic choriomeningitis. The method is described in detail.

STOESSER, Minneapolis.

REPEATED VACCINATION OF MAN AGAINST THE VIRUS OF EQUINE ENCEPHALOMYELITIS. DOROTHY BEARD, HAROLD FINKELSTEIN and J. W. BEARD, J. Immunol. **40**:497 (April) 1941.

Man, like other animals tested, reacts with a high titer of antibodies when given a primary vaccination with the virus of equine encephalomyelitis. Eastern strain virus almost invariably produced antibodies which disappeared in nine months. Western strain virus, however, produced antibodies which were usually little decreased after nine months. Subsequent vaccinations produced relatively longer periods of high titer.

BILLINGTON, Seattle.

TOCOPHEROL LEVEL IN SERUM OF NORMALS AND PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS. ISRAEL S. WECHSLER, GERA GERNSHEIM MAYER and HARRY SOBOTKA, Proc. Soc. Exper. Biol. & Med. **47**:152 (May) 1941.

Study of the level of tocopherol in the serum of 12 normal persons 23 to 30 years of age by a method employing a photoelectric colorimeter revealed an average value of 0.96 (range 0.59 to 1.62) mg. per hundred cubic centimeters. Four patients with amyotrophic lateral sclerosis who had not had tocopherol previously had values of 0.76 (range 0.52 to 1.00) mg. per hundred cubic centimeters of serum. A rise in the tocopherol level of the serum occurred when vitamin E was given orally, but the degree of increase did not correspond to the subjective or objective signs of improvement.

HANSEN, Minneapolis.

SYMPTOMS OF TUMOR (PROBABLE GLIOMA) CURED BY RADIOTHERAPY, WITH CHECK-UP AFTER FIVE YEARS. P. LAMARQUE, H. VIALLEFONT and J. CHAPTAL, Bull. Soc. pédiat. de Paris **37**:146 (March) 1939.

A boy who began to show symptoms of a tumor of the left frontal lobe at the age of 7½ years received high voltage roentgen therapy, as the parents refused to

permit operation on him. His condition was much improved five days later. On the return of some symptoms the following year, similar therapy was given. Because of the marked radiosensitivity the tumor was believed to be a medulloblastoma. When observed after a period of five years he was apparently well.

BENJAMIN, Montreal, Canada.

FAMILIAL OCCURRENCE OF PRURITUS, URTICARIA AND PARESTHESIAS WITH HYPERKINESIS OF THE LOWER EXTREMITIES. J. C. MUSSIO-FOURNIER and F. RAWAK, Confinia neurol. **3**:110, 1940.

Mussio-Fournier and Rawak describe a syndrome found in 3 members of one family. The clinical manifestations were pruritus, urticaria and hyperkinesis of the lower extremities caused by paresthesias appearing during rest. While other members of the same family also showed allergic reactions, the authors express the belief that the present symptoms were not specifically allergic but were secondary to heredodegeneration of the nervous system.

DE JONG, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.]

CONGENITAL ENCEPHALOPATHIES IN CHILDHOOD. A. ARIZTIA, Rev. chilena de pediat. **11**:251 (May) 1940.

Consideration of the etiology of cerebral palsy in childhood requires the collaboration of the pediatrician, the neurologist and the pathologic anatomist. A number of factors must be considered, including hereditary ones which may endanger the intrauterine existence of the fetus and may have serious effects on the germ plasm, cachectic disease of the mother during pregnancy and the toxic conditions. Transplacental infections, such as syphilis and familial icterus gravis, are among the extrauterine factors. Conditions affecting the nervous system of the child, such as encephalitis and infections, encephalopathies or convulsions, are important. The simple explanation heretofore given of the causation, namely, that the condition is due to syphilis or to obstetric trauma, is not adequate. There are many early clinical symptoms, such as feeding difficulties, retarded development and a tendency to prolonged hyperthermia. All of them are probably of central nervous system origin.

In some patients great weakness and tropholability and hydrolability are early expressions of this condition. The neurologic manifestations may not appear for months. Physical retardation commonly occurs.

The disorder is not progressive and changes little from the date of its development. In the treatment adequate diet and hygiene, massage and proper gymnastics may ameliorate many of the symptoms. The patients always present a special pedagogic problem which cannot be managed in the ordinary school.

The author recommends provision of special schools for the afflicted children. As a prophylactic measure he recommends interruption of pregnancy in women who have incurable physical disorders or advancing cachexia. In the case of familial icterus gravis the mother and the newborn infant should receive the proper treatment. Greater care should be used in obstetric procedures, and traumatizing measures should be guarded against if possible. The author believes it of special importance to educate midwives better.

SCHLUTZ, Chicago.

NORMOCALCEMIC TETANY (SPASMOPHILIA). ALEX GIEGEL, Arch. f. Kinderh. **118**:11 (Sept. 26) 1939.

Giegel reports the case of a 4 year old girl with carpopedal spasms and pitting edema of the dorsum of the left hand. The nerve response to the galvanic current was increased, but Chovstek's sign and the peroneal phenomenon were absent. The concentrations of calcium and phosphorus in the serum were in the normal range. A hormonal disturbance was suspected.

Two months after the patient was first examined a luxation of the first metacarpal bone of each hand was noted. Roentgen examination of the child's mother revealed a similar abnormality. For this reason the diagnosis of Madlung's disease is suggested.

ARON, Chicago.

OTITIC HYDROCEPHALUS WITHOUT PAPILLARY EDEMA. C. C. BAGER, Ugesk. f. læger **102**:338 (April 4) 1940.

After a mild purulent otitis a 7 year old boy displayed severe symptoms and signs of cerebral disease with involvement of the posterior cranial fossa. At the operation inflammatory changes were found on the posterior surface of the pyramid. Puncture of the dura mater produced a large quantity of fluid. Remarkable clinical improvement and an uneventful recovery followed.

WALLGREN, Göteborg, Sweden.

Psychology and Psychiatry

THE CHILD'S EMOTIONAL AND SOCIAL ADJUSTMENT. CAROLINE B. ZACHRY, Proc. Sixth Conf. Educ. & Exceptional Child, May 1940, p. 8.

The author indicates that social adjustment and emotional growth go hand in hand. She points out some of the larger stages of emotional growth and the conditions that stimulate or hinder them.

BEVERLY, Chicago.

THE VALUE OF THE MOTION PICTURE IN EDUCATION WITH SPECIAL REFERENCE TO THE EXCEPTIONAL CHILD. A. A. BRILL, Proc. Sixth Conf. Educ. & Exceptional Child, May 1940, p. 15.

Motion pictures are of value to children and adults because they serve as emotional outlets for their pent-up feelings (resentments, wishes, etc.). The author states: "I have never seen, never in all my psychiatric experience, any male or female, who ever committed any crime because of having seen or read something."

BEVERLY, Chicago.

STUDIES ON A GROUP OF CHILDREN WITH PSYCHIATRIC DISORDERS: I. ELECTROENCEPHALOGRAPHIC STUDIES. HANS STRAUSS, W. C. RAHM JR. and S. E. BARRERA, Psychosom. Med. **2**:34 (Jan.) 1940.

This is a report of electroencephalographic studies on 44 children who were referred to a psychiatric institute because of behavior problems. In spite of the nosologic confusion in which the authors become involved, they present strong evidence of the organic basis of some behavior disorders.

Thirty (68 per cent) of their subjects had definite abnormal electroencephalograms. The usual clinical methods of investigation failed to reveal focal organic pathologic change in the brain in a significant number of these children.

An important observation was that none of the 14 children with normal electroencephalograms had an intelligence quotient of less than 80 but that 33 per cent of those with intelligence quotients below 80 had abnormal electroencephalograms.

WEINFELD, Highland Park, Ill.

OVARIAN INSUFFICIENCY IN MOTHERS OF MONGOLIAN IDIOTS. HEIN SCHRÖDER, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:148 (Aug.) 1940.

Schröder was interested in checking the findings of Geyer, who, in a monograph on the cause of mongolian idiocy (Leipzig, Georg Thieme, 1939), stated that he found evidence of ovarian insufficiency in 29 of 33 mothers of mongolian idiots. Schröder studied 60 mothers of mongolian idiots from the gynecologic and endocrine

standpoints. He also studied the mothers of 60 normal children. In 11 of the 60 mothers of mongolian idiots various disturbances were found which pointed to ovarian insufficiency. Similar evidence of dysendocrinism was found in 18 of the control mothers. Ovarian insufficiency is therefore not more common in mothers of mongolian idiots than in other women. Geyer's hypothesis that the ovarian insufficiency causes an injury to the ovum is untenable.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

Diseases of the Genitourinary Tract

THE COMPARATIVE NUTRITIVE EFFICIENCY OF INTRAVENOUS AMINO ACIDS AND DIETARY PROTEIN IN CHILDREN WITH THE NEPHROTIC SYNDROME. LEE E. FARR, KENDALL EMERSON and PALMER H. FUTCHER, J. Pediat. **17**:595 (Nov.) 1940.

Nitrogen balance studies of ten weeks' duration on 4 children with the nephrotic syndrome are reported. Replacement of 33 to 57 per cent of dietary protein nitrogen with nitrogen furnished by casein hydrolysate given intravenously slightly increased the efficiency of nitrogen utilization in these patients and within this range of substitution indicated that casein hydrolysate completely replaced dietary protein. Intravenous administration to these nephrotic children of 30 to 42 Gm. of casein hydrolysate daily during alternate weeks for four injection periods was not followed by consistent increases in the concentration of plasma amino acids or plasma proteins. The injections did not prevent the occurrence of nephrotic crises, but they did effect a rise in urea clearance. There was no evidence that the intravenous administration of casein hydrolysate shortened the course of the nephrotic disease in these patients, significantly affected in a favorable manner the severity of the nephrotic signs or symptoms of the disease or influenced the ultimate outcome favorably. However, the authors found that intravenous injections of amino acids are of definite value in the therapy of complications arising in nephrotic crises, notably bacteremia.

RAUH, Cincinnati.

PUBERTAL MENSTRUAL DISTURBANCES. EVA MÜLLER, München. med. Wchnschr. **88**:428 (April 11) 1941.

This is a further comment on the problem of menstrual disturbances in girls in labor camps. Dr. Müller does not agree with all the statements of Professor Albrecht which recently appeared in the *Münchener medizinische Wochenschrift.* Dr. Müller is employed in the Berlin office which supervises the health of the work camp personnel. She states that each girl keeps a record of the time and duration of her menstrual periods and that the records are supervised by the camp doctor. From over 7,000 such yearly records it was found that 30 per cent of the girls had some disturbance in the regularity of their periods. The duration was one month for 17.3 per cent, two months for 7.2 per cent and three months for 2.7 per cent. When the amenorrhea lasts more than three months the patient is referred to a gynecologic clinic for examination and treatment. Dr. Müller points out that endocrine therapy is not denied girls from labor camps, if such treatment is advised. The cost of sickness of workers in labor camps is defrayed from a special fund, independent of the regular health insurance funds.

BRAHDY, Mount Vernon, N. Y.

NEUROCYTOMA OF THE KIDNEY. H. H. LOUCKS and K. Y. CHIN, Chinese M. J. **59**:212 (March) 1941.

The authors report the case of a Russian girl, 9 years old, admitted to the hospital for obesity which dated back to 5 years of age. There was no functional disturbance of the brain and the eyes, and the somatic measurements were within

normal limits. The blood pressure was 120 systolic and 80 diastolic. The sugar tolerance was increased. The sella turcica and the bones were normal.

After admission to the hospital the child began to cough, with fresh blood in the sputum; the roentgenogram of the lower lobe of the left lung showed a uniform clouding, due to pleural pus. Both the pus and the sputum contained hemolytic streptococci and type IV pneumococci. Drainage finally resulted in healing. Two years later there appeared a symptom complex of pain in the extremities of the right side, frontal headache, disturbed vision and repeated vomiting, which persisted for six weeks before the child reentered the hospital. At this time she was obese and had low fever, and a soft, not tender swelling was evident over the occipital region; a mass was felt in the left upper quadrant of the abdomen; the right shoulder was swollen and tender; moderate leukocytosis and anemia were found. The roentgenogram of the skull was normal, although there was suggestion of a slight increase of pressure. Positive findings were noted in roentgen examinations of the various other portions of the body, especially a mass which displaced the left kidney upward. Soon a biopsy of tissue from the right humerus showed carcinomatous metastasis. Roentgen treatment was without avail; other metastases appeared. The anatomic diagnosis of the growth was neuroblastoma of the left kidney with general metastasis. Under the microscope the tumor showed only one type of tissue, which was a diffuse sarcomatous growth of small dark-staining cells with many large and small pseudorosettes. The authors discuss the roentgenologic diagnois, the pathologic picture and the path of development in this case.

NEFF, Kansas City, Mo.

EMBRYONAL MIXED TUMOR (WILMS' TUMOR) OF KIDNEY. I. SNAPPER and S. D. WU, Chinese M. J. **59**:223 (March) 1941.

For two months a Chinese boy of 15 years had been aware of a growing mass in the abdomen which was productive of intermittent pain in the left flank. The growth soon occupied the whole left side of the abdomen. There were fever, cardiac palpitation, shortness of breath and coughing.

Cachexia was marked, the face flushed and the lymphatic gland slightly noticeable; there was no change in the skull or eyes. The urine contained a small amount of albumin, urobilin and many red and occasional white corpuscles. Examination of the blood showed that there was anemia, and the result of the phenolsulfonphthalein test was 55 per cent at two hours; but there were no abnormal cells in the blood smear. The sedimentation rate was much increased. The patient had severe abdominal pain.

The clinical discussion is by Snapper. He differentiates this tumor from a neuroblastoma of the adrenal gland, which contains bone metastases, especially in the orbit and skull, and in which there is no blood in the urine. Operation in such cases rarely prevents metastases, which may be due to the fact that the children are usually brought in at a very late stage of the disease. An early operation has occasionally permitted the patient to survive.

NEFF, Kansas City, Mo.

A CASE OF SARCOMA OF THE OVARY IN A GIRL. T. KIKUTI and Y. MINAKAWA, Jap. J. Obst. & Gynec. **23**:299 (Dec.) 1940.

A primary sarcoma of the ovary was found in an 11 year old girl. During four months of observation the sarcoma increased to several times its original size. Because of adhesions, it could not be removed surgically and radiotherapy was instituted. The primary lesion disappeared after therapy, but within a short time after cessation of treatment metastases were discovered in the liver and the lungs.

POTTER, Chicago.

Is Venereal Lymphogranuloma Hereditarily Transmitted from the Sick Mother to Her Fetus? C. E. Sonck, Nord. med. **5**:371 (March 2) 1940.

Sonck has made a follow-up study of 19 infants born of mothers suffering from venereal lymphogranuloma. Fourteen of the children were examined and found healthy, and for 12 of them the Frei test was carried out and the reaction found to be negative. The remaining 5 infants were free from morbid symptoms according to information from the mothers. In contradiction to this result, Sonck reports that he has observed 6 small girls suffering from lymphogranuloma venereum who were probably infected by their mothers and that in the case of none of these children was there any suspicion of congenital disease. Sonck is therefore of the opinion that venereal lymphogranuloma, at least usually, is not hereditarily transmitted.

Wallgren, Göteborg, Sweden.

Prognosis of Hypernephroma. R. Johannsen, Beitr. z. klin. Chir. **170**:136, 1939.

The prognosis is very poor because symptoms usually appear very late (hematuria, pain or a palpable mass appears after most of the damage has been done). Education of physicians to look thoroughly into the matter by roentgenographic, urographic or cystoscopic examination as early as possible is necessary.

Rubin, Boston.

Gonorrheal Vulvovaginitis Successfully Treated with Sulfapyridine. Anders Smith, Nord. med. **4**:3880 (Dec. 30) 1939.

A 5 year old girl who was infected with gonorrhea by a maid, was at first treated with dimethyldisulfanilamide (N^1, N^1-dimethyl-N^4-sulfanilylsulfanilamide) without any demonstrable effect. After she was given sulfapyridine a rapid recovery set in.

Wallgren, Göteborg, Sweden.

Treatment of Nocturnal Enuresis. C. N. S. Gundtoft, Ugesk. f. læger **102**:483 (May 9) 1940.

The author reports on successful treatment of bedwetting with a fluid extract of ergot given half an hour before the child goes to bed.

Wallgren, Göteborg, Sweden.

Diseases of the Ductless Glands; Endocrinology

Pinealectomy in Successive Generations of Rats. W. E. Sullens and M. D. Overholser, Endocrinology **28**:835 (May) 1941.

Studies by other investigators have shown that administration of extract of beef pineal bodies to successive generations of rats results in retardation in growth and acceleration in development, both of which become more marked with each succeeding generation.

Here the reverse of the above experiment is reported. Pinealectomy of 3 successive generations of parent rats at the ages of 20 to 21 days produced no appreciable effect on the body weight, the body length, the rate of development or the histologic structure of the endocrine glands of the offspring.

Jacobsen, Buffalo.

Activities of the Food and Drug Administration in the Field of the Sex Hormones. Jack M. Custis and Ewald Witt, J. Clin. Endocrinol. **1**:363 (April) 1941.

Methods of assaying estrogens, progestins and gonadotropins are described. The percentage of commercial preparations failing to meet legal requirements is given, and the need for more intensive effort to detect inert preparations is pointed out.

Jacobsen, Buffalo.

IMMUNITY IN DIABETES: III. RELATION OF TISSUE GLYCOGEN AND BLOOD CHEMISTRY TO BACTERIAL DISSEMINATION, ANTIBODY FORMATION AND SURVIVAL AFTER INFECTION IN DIABETES. RUSSELL RICHARDSON, J. Clin. Investigation **19**:239 (Jan.) 1940.

In normal rabbits and in depancreatized cats a significant correlation was demonstrated between the concentration of glycogen in the liver and the survival time after intravenous inoculation with bacteria. Acidosis appeared to increase the frequency with which the dissemination of bacteria occurred after intradermal inoculation.

GUEST, Cincinnati.

EXOPHTHALMOS IN GOITRE. N. M. HARRY, M. J. Australia **1**:412 (April 5) 1941.

The author gives an account of the etiology, pathology and clinical features of both exophthalmos and lid retraction in goiter. In the past, little attempt has been made to distinguish between true exophthalmos and apparent exophthalmos, which is caused by widening of the palpebral fissure due to retraction of the upper eyelid. The two may be associated, but frequently lid retraction is present alone. Many of the classic "signs" are indicative of spasm of the nonstriated muscular portion of the levator palpebrae superioris, rather than of proptosis.

Evidence is presented which indicates that in goiter the pituitary and thyroid gland factors acting either alone or combined may bring about exophthalmos. In typical cases of toxic goiter the thyroid hormone factor is dominant, and the protrusion of the eyeball is due in large measure to vascular hyperemia in the orbit, often associated with edema of the periorbital fat. However, the excessive tone of the plain muscle in the upper eyelid (Muller's muscle) may result in lid retraction and apparent exophthalmos.

Paradoxic or severe progressive exophthalmos, which occurs both in toxic goiter and independently of it, is due to excessive secretion of pituitary thyrotropic hormone. The eyeball in such cases is as a rule extruded because of the increased volume of the extrinsic ocular muscles and lacrimal glands. Methods of treatment of this rare but dangerous condition are outlined.

GONCE, Madison, Wis.

CASE OF PROGERIA. RUTH KORSGAARD, Ugesk. f. læger **102**:309 (March 28) 1940.

Progeria was diagnosed in a 13½ year old girl. The principal features were: unsatisfactory physical development, senile appearance, fragile hair (partially very sparse), anomalous teeth with gingival atrophy and dry skin. There was normal excretion of sweat and sebum by the skin and no rhinitis. The basal metabolism and the hormonal excretion were normal. The usual laboratory examinations gave normal results. The mental age corresponded to the chronologic age. The parents and 4 sisters and brothers were normally developed.

WALLGREN, Göteborg, Sweden.

Diseases of Muscles, Bones, Joints and Lymph Glands

OCULAR FINDINGS ASSOCIATED WITH DYSOSTOSIS MULTIPLEX AND MORQUIO'S DISEASE: REPORT OF A CASE OF THE FORMER. C. A. VEASEY JR., Arch. Ophth. **25**:557 (March) 1941.

A boy 18 months old presented a typical picture of dysostosis multiplex. The mentality was subnormal. The head was large and square, with prominent frontal bones. The bridge of the nose was broad and depressed. Nasal breathing was obstructed, and a mucopurulent discharge was present in the nose. The palatal arch was high and narrow. The tonsils were small, but the adenoids were large.

The eyes were set far apart. The corneas were hazy and appeared large but were not. The pupils were normal but did not dilate fully after instillation of a mydriatic. The optic nerves and retina were normal. The vision was apparently good.

WESCOTT, Chicago.

THE IMPORTANCE OF GROWTH ARREST LINES IN RADIOLOGICAL DIAGNOSIS AND PROGNOSIS. JOHN A. SIEGLING, Illinois M. J. **79**:468 (June) 1941.

Lines appearing in the roentgenograms of long bones not only reveal much of the physiology of bone growth but also assist materially in the diagnosis of certain conditions and to some extent foreshadow the future of lesions about the epiphyses.

BARBOUR, Peoria, Ill.

THE TREATMENT OF FIBROSITIS AND ALLIED DISORDERS BY LOCAL ANESTHESIA. M. KELLY, M. J. Australia **1**:294 (March 8) 1941.

In the majority of cases of somatic pain the offending lesion is a nodule situated in muscular tissue, which can be recognized as a strictly localized area of acute tenderness, causing widely distributed referred pain and deep tenderness. In some cases subcutaneous edema is caused. In the limbs these reactions are prone to be referred to the joints. Infiltration of the nodule with a local anesthetic, such as 5 to 15 cc. of nupercaine solution (1 : 1,500), immediately abolishes both the acute localized tenderness and the diffused pain and tenderness. In the majority of cases the relief is permanent. These observations shed a new light on the pathology of the group of diseases known as fibrositis and allied rheumatic infections. Emphasis is laid on the importance of the part played by the nocifensor nervous system in the symptomatology of rheumatism.

GONCE, Madison, Wis.

MARBLE BONES (ALBERS-SCHÖNBERG) DISEASE. H. KRAMER, München. med. Wchnschr. **88**:132 (Jan. 31) 1941.

Kramer describes a case of marble bones in a man 26 years of age. Another physician informed the author that a 28 year old brother of the patient had the same condition. Four other siblings were well. Examination of the patient's blood revealed a mild anemia, 5,200 leukocytes with the following differential count (in percentages): segmented cells, 34; stab cells, 4; lymphocytes, 22; eosinophils, 4; basophils, 1, and myelocytes, 35. The high percentage of myelocytes persisted and could not be explained. Roentgenograms established the diagnosis of marble bone disease. The author states that about 40 cases have been described; however, no American references are given. BRAHDY, Mount Vernon, N. Y.

OSTEOGENESIS IMPERFECTA AND ITS EUGENIC SIGNIFICANCE. H. J. LOESCHE, München. med. Wchnschr. **88**:162 (Feb. 7) 1941.

Clinically osteogenesis imperfecta is characterized by pathologic fractures, blue scleras and occasionally otosclerosis. Endochondral and periosteal bone formation is defective owing to poorly functioning osteoblasts. No disturbance of the mineral metabolism has been demonstrated. The disease affects not only the bones but all supporting tissue of mesenchymal origin. The author believes that osteogenesis imperfecta is transmitted as a dominant characteristic.

Loesche reports the case of a pregnant woman whose father and grandfather had multiple fractures. She had 4 spontaneous deliveries. Two of her children were well, but the other 2 had sustained numerous fractures. She showed some symptoms associated with osteogenesis imperfecta, and a roentgenogram revealed an old fracture of the neck of one femur. The transmission of such a disease to offspring would be detrimental to the race. Legal permission to interrupt the

pregnancy and sterilize the patient was requested from the court which decides such matters. Legal permission was granted. The author feels that there were sufficient medical indications for the procedure aside from the question of eugenics.

BRAHDY, Mount Vernon, N. Y.

Diseases of the Eye

LEPTOTRICHOSIS CONJUNCTIVAE (PARINAUD'S CONJUNCTIVITIS) WITHOUT GLANDULAR INVOLVEMENT: REPORT OF A CASE. F. H. VERHAEFF, Arch. Ophth. **25**:1 (Jan.) 1941.

Among the 56 cases of leptotrichosis conjunctivae observed by Verhoeff this is the only one in which there was no glandular involvement. The author was unable to find any similar case reported in the literature. The patient was a 28 month old boy.

WESCOTT, Chicago.

CONGENITAL RETINAL FOLDS AND MICROCEPHALY: REPORT OF A CASE. SAMUEL GARTNER, Arch. Ophth. **25**:93 (Jan.) 1941.

Thirty-eight cases of congenital retinal folds have been described in the literature under various titles. Such a fold usually arises at the optic nerve head and extends to the ora serrata. The author reports in detail the case of a 19 year old youth first examined at 4 months who had in addition microcrania, microcephaly and subnormal mentality.

WESCOTT, Chicago.

DRUSEN OF THE OPTIC PAPILLA: A CLINICAL AND PATHOLOGIC STUDY. BERNARD SAMUELS, Arch. Ophth. **25**:412 (March) 1941.

A résumé of a microscopic study of preparations from twenty globes in which drusen of the papillae were found is presented. The condition is found at all ages, but the youngest in this series was 10 years of age. The drusen may appear singly or in clusters and may be pigmented or nonpigmented. They do not affect vision unless found posterior to the choroidal ring.

WESCOTT, Chicago.

DICTYOMA IN AN EARLY STAGE: REPORT OF A CASE. HARRY IMRE, Arch. Ophth. **25**:629 (March) 1941.

This is a detailed report of the microscopic examination of an eye of a 2 year old boy. The examination resulted in a clinical ophthalmologic diagnosis of intraocular tumor, cataract and secondary increase in tension. To this type of tumor Fuchs in 1908 gave the name dictyoma.

WESCOTT, Chicago.

TREATMENT OF RETINITIS PIGMENTOSA WITH RETROBULBAR INJECTIONS OF ATROPINE SULFATE. W. MAX BROWN, Arch. Ophth. **25**:819 (May) 1941.

Because retinitis pigmentosa begins in the equatorial region of the fundus, in the area of poorest vascularity, the author believes that the principle of vasodilation is important. Six patients were treated with retrobulbar injections of a 1:1,000 solution of atropine sulfate and followed for two years. Two showed definite improvement; the condition of 1 was apparently arrested and 3 showed no improvement.

WESCOTT, Chicago.

Skin Diseases; Allergy

SENSITIVITY TO CASEIN IN INFANTILE ECZEMA CONFIRMED BY BIOLOGIC TITRATION OF THE TESTING EXTRACT. LEWIS WEBB and HENRY N. PRATT, J. Allergy **12**:143 (Jan.) 1941.

The authors report a series of experiments to show that a small proportion of children with eczema are sensitive to casein.

The authors believe that "the plan of diet to be followed in dealing with individuals hypersensitive to milk depends, to a considerable degree on the presence or absence of casein sensitivity."

HOYER, Cincinnati.

DEFINITIONS OF WORDS PERTAINING TO ALLERGY. J. Allergy **12**:202 (Jan.) 1941.

This article is the report of a committee on nomenclature prepared April 20, 1939 for the Association of Allergy Clinics of Greater New York. Dr. William S. Thomas was chairman of the committee

HOYER, Cincinnati.

SUDDEN DEATH IN INFANTILE ECZEMA. J. H. TWISTON DAVIES, Brit. J. Dermat. **52**:182 (June) 1940.

The author reports 3 cases of this redoubtable complication in order to discourage light-hearted hospitalization. In similar cases previously reported death has been attributed to cross infection, status thymicolymphaticus and anaphylactic shock. None of these conditions apparently played a role in the cases reported. In cases of this kind death occurs, as a rule, within a few days after separation of the child from the mother and irrespective of treatment, nursing or nutrition. The author hints that perhaps psychologic disturbances may play a causative role. He poses the question: "Can it be that the eczema in an infant is perhaps compensated by certain profound systemic and humoral adjustments, and that sudden removal of both the psychological stimulus and the eczema itself leads to a fatal upsetting of this balance?" In 2 of the cases reported it was clear that the mother did not particularly want the child.

RATTNER, Chicago. [ARCH. DERMAT. & SYPH.]

NAPKIN AREA RASHES. L. FORMAN, Practitioner **146**:238 (April) 1941.

The conditions discussed are: (1) simple napkin erythema due to local irritation by ammoniacal urine and soiled napkins; (2) infective dermatitis, produced by the fecal streptococcus or by Monilia albicans; (3) impetigo contagiosa; (4) scabies.

The incidence of the first three of these eruptions depends on the standard of cleanliness maintained with the baby and with the napkins, and on the care with which feeding is supervised.

In considering the differential diagnosis of these varieties of dermatitis affecting the napkin area, the severity and the site of maximum involvement of the skin will give the clue as to its infective nature. Simple napkin erythemas of this area leave the folds untouched, whereas in the infective varieties the condition is at a maximum in the folds. The deeper red color, the defined edge, and the presence of blisters suggest a monilia rather than a streptococcal dermatitis. The small discrete papules which may complicate a napkin erythema, seen over the buttocks, may give rise to the suspicion of congenital syphilis, which, although rare in both hospital and private practice, must always be borne in mind.

Impetigo contagiosa may occur on the buttocks, though lesions are more usually seen on the face, limbs and hands. The causal organism is commonly the Staphylococcus aureus, but hemolytic streptococci may be responsible. The infection may be acquired from an adult who has a whitlow or boil or, if the child is in an institution, from infected clothing or napkin. Spread thus occurs as in pemphigus neonatorum, which is in fact a staphylococcic impetigo.

Scabies is very much on the increase. The buttocks are one of the sites of election both in infants and in children. Maceration of the skin and warmth of the skin under the napkin will favor the spread of the infestation in this area. Small papules, the size of a split pea, scratch marks and runs will be seen. In infants, the latter are more commonly seen on the palms and soles (in contradistinction to what is observed in adults). On the lower part of the abdomen

and the genitals, excoriations, papules and diffuse dermatitis occur. Other members of the family may show evidence of scabies. Dermatitis of the nipples or infiltrated papules on the areola in the mother will suggest the diagnosis.

GELSTON, San Francisco.

SYMPTOMS AND ETIOLOGY OF CONGENITAL ECTODERMAL DYSPLASIA. K. J. BORGGREVE and I. COHEN, Dermatologica **82**:25, 1940.

A boy, an only child, showed the typical syndrome of congenital ectodermal dysplasia with anhidrosis, hypotrichosis and deficient dentition. Histologic examination of skin from the back showed normal skin without sweat glands, sebaceous glands or follicles. The boy had attacks of fever, which may be explained by a lack of thermic regulation; they could be reproduced by exposure to an arc lamp. The boy suffered frequently from eczema. A cousin had a congenital cataract. The Wassermann, Sachs-Georgi, Kahn, Meinicke and citochol reactions were negative. His maternal grandmother had acquired syphilis after the birth of her fourth child. The mother, who was the sixth child, and 2 of her sisters had congenital syphilis but no ectedormal dysplasia. Fournier's "parasyphilis" may be of etiologic significance in this case.

HELEN O. CURTH, New York. [ARCH. DERMAT. & SYPH.]

Teeth and Dentistry

FORENSIC ASPECTS OF THE TEETH AND JAWS. EVELYN SPRAWSON, Proc. Roy. Soc. Med. **34**:1 (Nov.) 1940.

The president in her address discusses what may be learned of the age, habits and life history of the person from the study of the teeth and jaws. Age may be assessed with relative but not absolute accuracy, chiefly from the teeth and to a lesser extent from the jaws. After discussing age, the author then mentions diseases of childhood, such as icterus gravis neonatorum, which results in green teeth. Hypoplasia of the deciduous teeth is usually merely evidence of deficiencies in the mother's diet. The more common trophic form of hypoplasia found in the permanent teeth is evidence of malnutrition, usually in the form of a dietary deficiency and often associated with rickets. The stigmas of congenital syphilis, affecting chiefly the permanent incisors, are pathognomonic to those who are familiar with them.

The manner of upbringing affects the jaws and indirectly the teeth of both dentitions. The jaws of the breast-fed child were wider than those of the bottle-fed child, and consequently there is more room for the correct alinement of the teeth.

Heredity and size of the teeth do not tell one much. Habits and occupation in a few cases may be shown on the permanent teeth. The notch seen in the clay pipe smoker is a mark not only of habit but also of sex. Also the small notches seen occasionally on the maxillary incisors of women caused by biting off ends of cotton instead of cutting them are a mark both of occupation and sex.

The paper is concluded by a discussion on dental diseases, abnormalities in the position of the teeth and conservative dental work.

WILLIAMSON, New Orleans.

Miscellaneous

TREATMENT OF LEAD POISONING WITH SODIUM CITRATE. SEYMOUR S. KETY and T. V. LETONOFF, Proc. Soc. Exper. Biol. & Med. **46**:476 (March) 1941.

Six patients with lead poisoning who had mild to severe clinical manifestations and abnormally high lead concentrations in the whole blood were given sodium citrate by mouth (2 to 4 Gm. for adults; 1 to 2 Gm. for children) three times

daily. In every instance there was a rapid disappearance of toxic symptoms and the concentrations of lead in the blood became normal. The therapeutic and prophylactic possibilities of this clinical agent are to be studied further.

HANSEN, Minneapolis.

CALCIFICATION OF THE HUMAN PLACENTA. M. MASTERS, J. Obst. & Gynec. Brit. Emp. **47**:437 (Aug.) 1940.

The amount of calcium in the placenta when birth occurred prematurely, at term and postmaturely was estimated by roentgen examination, chemical analysis and histologic examination. A close correlation was found among all methods. There is a significant increase in calcium in the mature and postmature placenta over that of the premature, but the average difference between the mature and the postmature is without statistical significance. The authors conclude that the increased mortality rates found among postmature infants cannot be due to excessive calcification of the placenta.

POTTER, Chicago.

BALNEOLOGY IN DISEASES OF CHILDREN. LOUIS LEIPOLDT, South African M. J. **14**:435 (Nov.) 1940.

Balneotherapeutic treatment is often exceedingly beneficial in convalescence from rheumatic fever, typhoid and especially lipid nephrosis. When heart muscle is involved, as in cases of chronic malaria, diphtheria and disorders of metabolism, such as pellagra, acrodynia, and the varieties of nutritional edema, thalassotherapy, which permits of surf bathing, is more useful.

The greatest benefit from thermal baths is obtained in cases in which the child has a high fatigue index.

HARTMAN, Cleveland.

Book Reviews

Communicable Disease Nursing. By Theresa I. Lynch, R.N., Ed.D. Price, $3.75. Pp. 678, with 156 illustrations. St. Louis: C. V. Mosby Company, 1942.

All those engaged in the teaching of student nurses will welcome this book, which is obviously the product of experience in teaching communicable disease nursing. The author does not limit her text to the care of these diseases in the hospital but includes instruction adaptable to the home and to the community. The material is concrete and well organized, and the entire book is written in a simple style, which is easy to read and which should make it easy for the student to grasp the knowledge quickly.

The subject matter includes the diseases suggested for the study in the "Curriculum Guide for Schools of Nursing," published by the National League of Nursing Education.

The book is divided into five parts as follows: "Orientation to Communicable Disease Nursing," "Medical Aspects and Nursing Care of Communicable Disease Nursing," "Tuberculosis," "The Venereal Diseases" and "Communicable Diseases and the Community." Each unit is divided into many chapters, at the end of which are a summary of "essential points to remember," a carefully selected bibliography and suggested readings. The appendix, divided into four parts, includes paragraphs on minor and uncommon communicable diseases with which the nurse should be acquainted and many summary reference charts based on the state sanitary code concerning the prevention and control of communicable diseases. These will be found invaluable to instructor and student alike. A glossary of terms pertaining to the subject matter is included, together with an excellent index. The chapter on "Infection and Resistance to Disease" should enable the nurse to overcome quickly her intense fear of communicable diseases. Chapter III presents control measures from the viewpoint of organized agencies, giving the nurse that knowledge of public welfare which is being increasingly demanded in her work. The short chapter on "Vaccines, Immune Sera and Serum Reactions" is commendable for the simplicity of its presentation. The eighty-two especially posed photographs throughout part I illustrate important general procedures and details in medical asepsis and give emphasis to the nursing application of the principles discussed in the chapter. Parts II, III and IV describe the "medical aspects and nursing care of communicable diseases." Forty-six diseases are grouped and classified according to their common manner of transmission. All discussions follow a fairly uniform trend in outline. Throughout these chapters there are drawings, photographs, charts and color plates to illustrate important phases of the subject matter. In part V, "Communicable Diseases and the Community," the author offers suggestions for improvised technics suitable for home and community.

Appendix E is well adapted to serve as a guide to organizing measures for admission and discharge of patients, physical examination, administration of antitoxin and immune serum, lumbar puncture, intubation and other important procedures. Twenty-eight nursing procedures are illustrated by photographs.

The book is nicely set up on semiglossy paper with unusually clear print and is attractively bound.

The general outline of teaching facilities, illustrative material and applied methods makes this book a valuable contribution to nursing.

Synopsis of Genito-Urinary Diseases. By Austin I. Dodson, M.D., F.A.C.S. Price, $3. Pp. 302, with 122 illustrations. St. Louis: C. V. Mosby Company, 1941.

This is the third edition of Dr. Dodson's book and has been brought up to date in regard to the new developments in urology. As the title implies, a

synopsis is given of the common urologic conditions. The book will be of value to the busy practitioner or the medical student or intern who wishes a quick handbook outline.

Urologic symptoms and findings are briefly discussed, but for a full knowledge of these conditions a broad training in medicine is presupposed.

Many minor urologic procedures, such as passage of catheters, sounds and bougies, are discussed.

Chapter 5, on nontuberculous infections, includes several valuable diets which are useful in acidifying the urine. A short résumé of the indications for treatment with sulfanilamide and its derivatives and for mandelic acid therapy is included.

There is a good, concise discussion of urinary calculi, including the new theories of renal calculus formation proposed by Randall. The effect of diet on calculus formation is discussed, and many comprehensive references are included, which will guide the reader to the most noteworthy work on calculous disease.

A chapter on neoplasm of the urinary tract gives the outstanding clinical characteristics of these conditions. The author gives the various methods of treatment and apparently feels that the choice of surgical or radiation therapy must be decided in each individual case.

This book serves to acquaint one with urologic conditions, but it is not comprehensive enough to serve as a source of diagnosis and treatment of urologic disease.

Rheumatic Fever in New Haven. Edited by John R. Paul, M.D. Price, $1. Pp. 176, with 22 tables and 45 charts. Lancaster, Pa.: Science Press Printing Company, 1941.

This book reports a study conducted over a twelve year period, from 1928 to 1940, as to incidence and prevalence of rheumatic fever in the city of New Haven.

It is comparable in type to several other such studies here and abroad. These studies all dovetail, and this one makes a valuable addition to conclusions in regard to this disease.

The chapter on epidemiology is a concise review of the present status of its obscure etiology.

The prevalence of rheumatic fever was determined by a survey of hospital admissions and of mortality statistics for juvenile heart disease and rheumatic heart disease among school children.

There are two interesting chapters in a statistical study of rheumatic heart disease among the well-to-do and rheumatic heart disease among the poor.

The rheumatic family has been carefully studied.

The last chapter, a general summary, is good and should convince one of the importance of rheumatic fever as a health problem.

The review shows a great deal of careful work and study and makes interesting reading.

Chinese Lessons to Western Medicine. By I. Snapper. Price, $5.50. Pp. 380, with 132 illustrations. New York: Interscience Publishers, Inc., 1941.

This is a most interesting book. While there is not a great deal of material specifically on pediatrics, nearly everything in it pertains in some way to pediatric work. Especially enlightening is the chapter "Nutritional Problems and Avitaminoses." The difference between the nutrition of the Chinese and that of the Western nations is such as to afford contrasts which are most enlightening. (Professor Snapper, it should be said, is head of the department of medicine in the Peiping Union Medical College, and these are personal observations from his clinic.) His observations on infectious diseases are also interesting, especially the chapter on kala-azar, which is prevalent in that region. The chapter on amyloid degeneration brings out points of much clinical interest. His observations on cardiovascular diseases and on anemia are stimulating. All in all, the book con-

tains a fund of experience which should be of a great deal of value in interpreting disease in this country because of its revelation of the way disease acts in China under very different conditions of hygiene and nutrition.

Infant Nutrition. By William McKim Marriott, B.S., M.D., revised by P. C. Jeans, A.B., M.D. Third edition. Price, $5.50. Pp. 475, with 31 illustrations. St. Louis: C. V. Mosby Company, 1941.

The third edition of this book by Marriott and Jeans reflects again the thoroughness which the authors have given to their studies of the problem. The first chapters deal with growth and development and metabolism, with a summary of the nutritional requirements during the period of infancy. Next the physiology of digestion and the character of the stools are considered. This is followed by a complete discussion of the different types of feeding. Nutritional disturbances and the various causes, especially infection, are well presented. The whole subject is rounded out with a consideration of special entities denoting some abnormality of nutrition, for example celiac disease, rickets, tetany and scurvy.

The material is presented in an easy, interesting style. The print and paper are excellent, and the index seems unusually complete.

Symptom Diagnosis. By Wallace Mason Yater, M.D. Fourth edition. Price, $10. Pp. 900, with 17 tables. New York: D. Appleton-Century Company, 1942.

This is the fourth edition of this book, originally written by Drs. Wilfred M. Barton and Wallace M. Yater. It is designed for quick reference work in the office and not for study. Symptoms are classified as regional and general. Under each symptom are paragraphs discussing briefly each disease or condition in which the particular symptom may be seen. A concluding paragraph lists the less common causes.

The whole field of medicine and surgery has been covered. Seventeen new tables of differential diagnosis have been inserted and the whole book brought up to date. The two indexes have been combined into a single index, which is a definite improvement. This book is one of the best of its kind.

Medicina infantil. Fifth Edition. By Juan P. Garrahan. Price not given. Pp. 1,150, with 215 illustrations. Buenos Aires, Argentina: El Ateneo, 1942.

The first edition of this pediatric textbook in Spanish was published in 1921. The present book is the fifth edition. It contains the usual subject matter found in such a volume and compares favorably with any pediatric textbook published in England or America at the present time. It is well organized, systematic and well written. The illustrations are well chosen. New and amplified material is given in chapters on the vitamins, infant feeding and bronchiectasis. Parts that have been amplified are discussions of the action of sulfanilamide and its derivatives, of treatment of pleural effusion and of choriolymphomeningitis. These amplifications bring this excellent textbook quite up to date.

Encephalitis. By Josephine B. Neal, A.B., M.D., Sc.D., F.A.C.P. Price, $6.75. Pp. 563, with illustrations New York: Grune & Stratton, 1942.

This volume brings the knowledge of encephalitis up to date. Written by Dr. Neal and her collaborators, all of whom have been studying the various aspects of the disease for a great many years, the clinical and pathologic pictures are vividly described in styles that are easily understood.

After a general description of the clinical manifestations of the various forms of the illness, succeeding chapters describe the epidemiology, clinical course, neurologic complications, sequelae, pathology and treatment. Every aspect of every form of the disease is described.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Pediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14[a], Utrecht, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Marique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Velado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico City.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico City.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Ernesto Vizcarrondo, Venezuela.
Secretary: Dr. E. Santos Mendoza, Venezuela.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Ave. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Atlantic City. Time: June 8-12, 1942.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edward C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Palmer House, Chicago. Time: Nov. 4-7, 1942.
Region I. Place: Bellevue-Stratford Hotel, Philadelphia. Time: April 1-3, 1942.
Region III. Place: Hotel Cleveland, Cleveland. Time: May 14-16, 1942.
Region IV. Meeting cancelled.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St, Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 30–May 2, 1942.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.
Place: Skytop Lodge, Skytop, Pa. Time: April 29-30, 1942.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 2:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. George M. Lyon, 955–4th Ave., Huntington, W. Va.
Secretary: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.
Place: Prescott. Time: April 1942.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Ernest Caulfield, 683 Asylum Ave., Hartford.
Secretary: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.
Place: Springfield. Time: May 19-21, 1942.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

Louisiana State Pediatric Society

President: Dr. Julian Graubarth, 3431 Prytania St., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1942.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Andrew G. Dow, 314 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Zahn, 2474 Valentine Ave., New York.
Secretary: Dr. Harry J. Cohen, 975 Walton Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Paul L. Parrish, 52 S. Oxford St., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.
Secretary: Dr. Leo S. Friedman, 3586 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Marsh M. Poole, 773 Fisher Bldg., Detroit, Mich.
Secretary: Dr. Donald J. Barnes, 773 Fisher Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Physician's and Surgeon's Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry S. Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. James M. Moser, 3751 Jenifer St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William A. Howard, 2222 Que St. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Alfred Langmann, 108 E. 68th St., New York.
Secretary: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHERN CALIFORNIA AFFILIATES

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barda, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. Ellsmer L. Piper, 3708–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway, 3720 Washington Blvd., St. Louis.
Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.